2018

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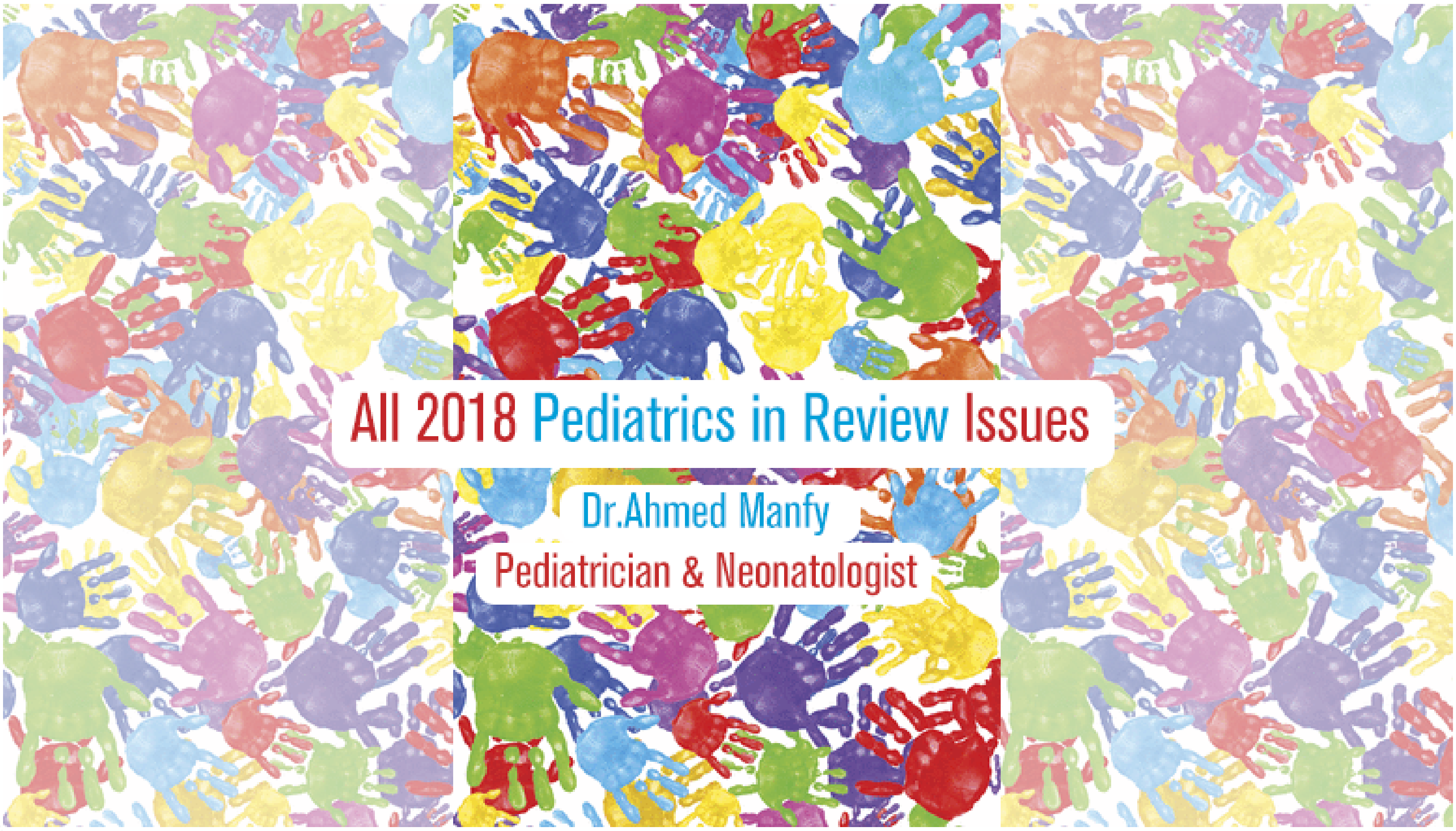

All 2018 Pediatrics in Review Issues

Dr.Ahmed Manfy
Pediatrician & Neonatologist

January, February, March, April,
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Urinary Tract Infections in Children

Balighian, Burke

Preparing Your Pediatric Patients and Their Families for the Operating Room: Reducing Fear of the Unknown

Adler, Leung, Lee, Dubow

Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Hyponatremia

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Synthetic Cannabinoids and Marijuana

The Who's Who of Usage

The use of synthetic cannabinoids has emerged as an important public health issue among high school students.

BY THE NUMBERS

9.4% of high school students ever used synthetic marijuana

61.1% of high school students did not use any type of marijuana

29.5% of high school students ever only used marijuana

The use of synthetic marijuana varied a little by region:

WEST 28.5%

MIDWEST 21.3%

NORTHEAST 17%

SOUTH 33.2%

1 in 10 high school students use synthetic marijuana

54% were in the 11th and 12th grades

RISKY BEHAVIORS

Students who use synthetic cannabinoids tend to engage in more risky behaviors than students who use marijuana only.

78.6% Currently use alcohol

46.2% Currently smoke cigarettes

70.7% Currently smoke marijuana

40.5% Have ever used hallucinogenic drugs

60.6% Have ever taken prescription drugs without a doctor's prescription

35.2% of those who have ever used synthetic cannabinoids used marijuana before age 13

Using synthetic marijuana 70.7%

Using only marijuana 51.5%

Using both

42.2% Female

57.8% Male

52.4% Non-Hispanic whites

11.4% Non-Hispanic blacks

28.4% Hispanic

PREVENTION

To prevent marijuana use and the use of synthetic cannabinoids, it is important that health professionals and school-based substance prevention programs include **strategies that reduce the initiation of marijuana and synthetic cannabinoid use**, particularly among students younger than 13 years.

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- Philip Fischer, MD, disclosed he has received honoraria from Relias Learning (AHC Media).
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- E. Steve Roach, MD, receives an honorarium from Elsevier for serving as editor of *Pediatric Neurology*.
- Miriam Weinstein, MD, is a paid consultant participating on the ad boards: for a new topical eczema product for Pfizer Inc.; and for a systemic eczema therapy for Amgen Inc.

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Predicting Earthquakes

This past year, in a talk on medical education, I discussed a short story I had read decades ago, "The Boy Who Predicted Earthquakes." In it, author Margaret St Clair writes of a 15-year-old boy named Herbert who can predict a calamity or miracle 48 hours before such an event actually occurs.

The boy successfully predicts election results, hurricanes, and earthquakes. However, his success depends on what he knows; he cannot make a prediction about something he has no knowledge of. He states, "… I can't predict anything unless I more or less know what it is …. That's the reason I read so many books. The more things I know about, the more things I can predict."

One can extrapolate this fictional character's quote to say that the more patients a clinician sees and the more he or she reads, the more clairvoyant that clinician becomes, predicting a patient's diagnosis on first glance.

I also gave a separate national talk this past year about a favorite academic exercise of mine. I enjoy case presentations, and I like to present a patient case in both a straightforward way (chief complaint, history of the present illness, review of systems, and physical and laboratory examination) and in a manner that manipulates the context of the patient's presentation, tweaking different aspects so as to possibly trigger a learner's rapid jump to the right diagnosis (Can you make a diagnosis by just listening to a sound? By asking only 1 history question after hearing the chief complaint? By viewing the patient from afar?).

The first method, which is really telling a story, teaches clinical diagnosis by sequentially revealing the whole tale, whereas the second method poses a mystery by giving sparse clues that, pieced together, may suggest a pattern that leads to a diagnosis. Both methods give learners "virtual" patient experiences that refine their diagnostic acumen, helping them to quickly make a true diagnosis when faced with the real disease.

As the short story asserts, the pattern prediction can be calamitous. For example, this past year, in reference to the pervasiveness of vaccine hesitancy, many articles in newspapers and journals spoke of the human propensity to see patterns where patterns truly do not exist, hence the persistence of the false theory that vaccines cause autism despite a preponderance of valid evidence that says otherwise.

Another example: Preparations for and responses to Hurricanes Harvey and Irma were significantly better thanks to the painful lessons learned after Hurricane Katrina hit New Orleans years ago. Two of our executive editorial board members were affected by the storms; they both wrote moving blogs for *Pediatrics in Review* about their personal experiences, reflecting on the good and not-so-good human responses to the aftermath. Whereas the emergency response to Harvey's and Irma's victims went surprisingly well overall, Puerto Rico's chaos after Hurricane Maria and Mexico's devastation after its major earthquake remind us that we don't always predict and prepare for hurricanes and earthquakes as well as we could and should.

AUTHOR DISCLOSURE Dr Zenel has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

"Earthquake-proofing" pediatric education requires similar foresight. Each autumn, the *Pediatrics in Review* editorial board meets during the annual American Academy of Pediatrics National Conference and Exhibition to review the state of the journal (a true *Pediatrics in Review* review), to reflect on the past year, and to advise on future directions. General pediatricians make up half the board, many different subspecialists make up the other half. At our most recent meeting, our subspecialist members tried to predict, based on their experience working with general pediatricians, what general pediatricians should know about upcoming advances in their subspecialties. Similarly, our general pediatrician board members expressed what they felt they should know in anticipation of the future of pediatric practice.

Both groups reaffirmed what core subjects we should continue to publish, and all members speculated how best to publish the journal in this digital world. The results of our own self-directed learning and improvement will appear in the journal in the upcoming monthly publications.

Pediatrics in Review has a great future, thanks to the editorial board, the editorial staff, and the readership. As deputy editor, Dr Hugh Allen provides thoughtful advice on the journal's direction. Drs Janet Serwint and Henry Adam, through the *In Brief* feature, provide succinct, practical articles on advances in pediatrics. In the feature *Index of Suspicion*, Dr Phil Fischer continues to spotlight cases that show common diseases that appear uncommonly and uncommon diseases that appear as common diseases. In *Visual Diagnosis,* Dr Mark Weems focuses on images that clue the reader toward a diagnosis. Dr Rani Gereige oversees the group of question writers who develop continuing medical education questions for our review articles, questions that now qualify for Part 2 Maintenance of Certification credit. The American Academy of Pediatrics publishing staff does an exemplary job of making sure that the journal is professional in appearance and content—and publishes on time. Thanks to reader input, we stay true to the journal's original purpose of publishing relevant, useful, and practical information in pediatrics.

New diseases and new gaps in medical knowledge will always appear. We really cannot predict when and where the next medical challenge will arise, but we can prepare for whatever it will be.

As the fictional Herbert said, "That's the reason I read so many books. The more things I know about, the more things I can predict." *Pediatrics in Review* will continue its efforts to provide accessible, up-to-date information to help you "predict earthquakes," so that you can truly help children when unexpected adversity appears.

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Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/safety-prevention/at-home/Pages/Earthquake-Disaster-Fact-Sheet.aspx

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Urinary Tract Infections in Children

Eric Balighian, MD,* Michael Burke, MD*

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Educational Gaps

Consideration of risk factors for urinary tract infections (UTIs) in young children with fever is critical for accurate diagnosis, as well as prevention of overtesting. The use of perineal bags to collect urine from young children should be limited to specific indications in the diagnosis of UTIs. Screening for and managing bowel and bladder dysfunction reduces the risk of UTIs in older children.

Objectives

After completing this article, readers should be able to:

1. Recognize the risk factors for urinary tract infections (UTIs) in children.
2. Review the interpretation of urinalysis and urine cultures.
3. Review antibiotic therapy choices for UTIs.
4. Describe which children need imaging after febrile UTIs.
5. Discuss prevention strategies to discuss with families.

CASE STUDY

Charlotte is a 13-month-old girl with a history of 2 febrile urinary tract infections (UTIs) 4 and 6 months ago. She had normal renal and bladder ultrasonographic findings 6 months ago. She presents with a fever that began yesterday. She has no other new symptoms. Her 4-year-old brother had a self-limited febrile illness 1 week ago, which resolved. At examination, she is fussy but consolable and alert. She is non–toxic appearing. Her physical examination findings show tachycardia with a heart rate of 130 beats/min, without murmur. Her respiratory rate is 28 breaths/min, without distress or retractions. Her lungs are clear bilaterally. Her tympanic membranes appear normal. Her abdomen is soft and nontender. Her genital examination findings appear normal, without erythema or labial adhesions. Her temperature is 102.5°F (39.2°C). A bag is placed to collect a urine sample. The urinalysis from the bag sample has 5 to 10 white blood cells (WBCs) per high-power field, a 1+ leukocyte esterase result, and a 1+ ketone result. Should a bag have been placed to collect urine? Does Charlotte have a UTI? How should she be treated at this point?

EPIDEMIOLOGY

UTIs are one of the most common bacterial infections in childhood, accounting for 5% to 14% of pediatric emergency department visits. (1) The prevalence of

AUTHOR DISCLOSURE Dr Balighian has disclosed no financial relationships relevant to this article. Dr Burke has disclosed that he serves as a section editor for *Contemporary Pediatrics*, a monthly publication by UBM Medica, and receives a stipend for this activity. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
CFU	colony-forming unit
DMSA	dimercaptosuccinic acid
IV	intravenous
UTI	urinary tract infection
VCUG	voiding cystourethrogram
WBC	white blood cell

UTIs and their effect on the health of children are substantial throughout childhood, from the neonatal period to late adolescence (2). Infants and toddlers cannot localize UTI symptoms, cannot submit spontaneous urine samples, and have other distinct characteristics when compared to children over 24 months of age; therefore, we will simplify this review of UTIs into 2 age groups: children less than 24 months of age (whom we will define as *infants and toddlers* in this review) and children 2 years of age and older.

Infants and Toddlers under 24 Months of Age

Roughly 7% of infants and toddlers who present with fever have a UTI. (1) Race, age, sex, circumcision status in male infants and toddlers, and other factors alter the prevalence. Knowledge of how these risk factors affect the likelihood of a UTI in a particular child is critical when assessing whether the child should ultimately undergo urine testing. When considering race, 10% of white febrile infants and toddlers without focal findings to suggest another source of infection will have a UTI, while 2% of black febrile infants and toddlers will have a UTI. (3) When considering sex and age, female febrile infants 12 months of age or less have a 6% to 8% prevalence of UTI, while febrile girls older than 12 months have a prevalence of 2%. The prevalence of UTI in febrile male infants is markedly affected by the circumcision status of the infant. Uncircumcised febrile male infants less than 3 months of age have a 20% risk of UTI, compared with a 2.4% risk in similar but circumcised male infants. In both circumcised and uncircumcised male patients, the prevalence of UTIs decreases with age. For example, circumcised febrile boys older than 12 months have a less than 1% risk of UTI. Additional factors, such as duration of fever, previous history of UTIs, and congenital anomalies of the urinary tract, alter the likelihood of UTI.

Children 2 Years of Age and Older

Children 2 years of age and older who present with urinary symptoms (dysuria, urinary hesitancy) have an overall 8% risk of UTI. (1) However, as in infants, important factors should be considered that modify risk. After 2 years of age, children are more able to report and localize specific symptoms, such as dysuria. The prevalence of UTI in boys 2 years of age and older is low, especially in circumcised boys. Important factors that affect prevalence in this age group include bladder- or bowel-withholding behaviors, congenital anomalies of the urinary tract, and previous history of UTI.

PATHOGENESIS

UTIs are usually caused when bacteria invade and ascend up the urinary tract from the urethra and into the bladder. Cystitis, a lower UTI, occurs when the infection and inflammatory response are localized to the bladder. Pyelonephritis is an upper UTI in which the bacteria and subsequent inflammatory response further ascend to the ureters and kidneys. Colonic bacteria are typically the culprits. *Escherichia coli* is the most common bacteria that causes UTIs in all ages, accounting for 54% to 67% of UTIs in children. *Klebsiella* (6%–7%), *Proteus* (5%–12%), *Enterococcus* (3%–9%), and *Pseudomonas* (2%–6%) are other common causative organisms. (4)

Hematogenous spread to the urinary system is a rare cause of UTI that can occur in neonates and children with immunodeficiency. Group B *Streptococcus, Staphylococcus aureus*, *Candida*, and *Salmonella* can cause pyelonephritis through the hematogenous route.

Mouse models have demonstrated that *E coli* attach to the superficial cells of the bladder lining, then invade the cells and multiply. These cells are shed in defense, which exposes lower layers of cells for bacterial invasion. These lower-layer cells that have bacteria could be the source of recurrent UTIs. Toll-like receptors are an important component of the host defense of UTIs. These toll-like receptors are on the surface of the bladder and activate the host inflammatory response by attracting WBCs to the surface of the bladder. (5)

CLINICAL PRESENTATION AND ESTIMATING RISK OF UTI

The clinical presentation of UTI varies with age. Infants generally present late in the course of infection because of initial nonspecific signs, such as fever, and the inability to express symptoms or localize pain. Older children can usually localize early symptoms of UTI, such as dysuria or abdominal pain, and therefore present earlier in the clinical course.

Infants and Toddlers under 24 Months of Age

Infants and toddlers under 24 months of age who have a UTI most often present with fever. Fever is a common and nonspecific symptom for which clinicians should consider UTI as an etiologic origin, especially when there are no other obvious signs or symptoms to suggest another diagnosis. Obvious signs such as a new rash may suggest a viral syndrome. Recent new respiratory symptoms, such as cough and congestion, suggest a respiratory infection. In the absence of other obvious symptoms, clinicians should be vigilant when assessing risk factors because about 7% of febrile infants and toddlers without an obvious source have a UTI. Clinicians should use the American Academy of

Pediatrics (AAP) Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 months of age when assessing risk of UTI in this age group. (6) The risk factors in Table 1 from the 2011 AAP Clinical Practice Guideline allow the clinician to evaluate the likelihood that a febrile infant has a UTI.

The guidelines use both a probability of UTI of up to 1% and up to 2% to allow clinicians to use their judgment in what is considered low risk and therefore to determine which children need to be further tested for UTIs. The probability of a UTI increases as the number of risk factors increases. The guidelines allow clinicians to calculate a pretest probability of UTI to make an informed decision about which children require further evaluation for UTI. Clinicians should also take into account other factors, such as ability to follow up and previous history of UTI, and include the family in the decision-making. If the decision is made to forego testing for UTI, follow-up is crucial, as risk factors such as severity and duration of fever may change.

TABLE 1. **Probability of Urinary Tract Infection Among Febrile Infant Girls and Boys According to Number of Findings Present**

PARAMETER	VALUE
Girls	
Individual risk factors	White race Age <12 mo Temperature ≥102.2°F (39°C) Fever ≥2 d Absence of another source of infection
Probability of urinary tract infection	
≤1%	No. of risk factors present: No more than 1
≤2%	No. of risk factors present: No more than 2
Boys	
Individual risk factors	Nonblack race Temperature ≥102.2°F (39°C) Fever ≥24 h Absence of another source of infection
Probability of urinary tract infection	
≤1%	No. of risk factors present: For circumcised boys, no more than 2.*
≤2%	No. of risk factors present: For circumcised boys, no more than 3. For uncircumcised boys: No additional risk factors.

**For uncircumcised febrile boys, probability of UTI exceeds 1% even with no risk factors other than being uncircumcised*

Risk factors for UTIs in female infants of this age group include white race, age less than 12 months, temperature greater than or equal to 102.2°F (39°C), and absence of another source of infection. The probability of UTI for male patients is most influenced by circumcision status. In febrile, uncircumcised male infants and toddlers under 24 months of age, the risk of UTI exceeds 1% without any additional risk factors.

Ill-appearing children who present with nonspecific symptoms such as fever have important additional diagnostic considerations that include bacteremia and sepsis. Ill-appearing children who warrant antibiotics because of the concern for a serious infection, such as sepsis, should be tested for a UTI. Urine specimens should be collected for urinalysis and culture because the antibiotics may treat an otherwise unknown UTI, masking the diagnosis from the clinician. Even though antibiotics for sepsis or bacteremia may adequately treat UTI, it is important to establish the diagnosis to determine antibiotic duration and choice, future risk of UTI, and possible preventative measures, as discussed in the management section.

Differentiating a lower UTI from an upper tract infection in infants on the basis of signs and symptoms is difficult, but if fever is present, most consider the infant to have upper tract involvement and therefore pyelonephritis. Laboratory values such as procalcitonin and C-reactive protein, when increased, have been shown to be helpful in assessing infants for renal involvement during an infection. (7) If further clarification is necessary, a dimercaptosuccinic acid (DMSA) scan can be performed. In a DMSA scan, DMSA is combined with a radionuclide to image the kidneys by using gamma cameras. A DMSA scan provides the best means of definitively identifying upper UTI but should not be routinely performed because typically, the management will not be altered on the basis of the results and because of radiation exposure related to DMSA. (8)

Infants less than 2 months of age are not included in the AAP guidelines. UTI should be considered for every febrile infant less than 2 months of age. Clinicians should be vigilant in assessing febrile infants less than 2 months of age for UTIs, even those with obvious respiratory symptoms. Infants in this age group with respiratory symptoms have an appreciable risk of UTI, with 1 study showing respiratory syncytial virus–positive febrile infants having a UTI risk of 7%. (9) In infants who present with symptoms of bronchiolitis or respiratory syncytial virus–positive bronchiolitis, 1 systematic review showed that the risk of UTI was 3.3%. (10)

Children 2 Years of Age and Older

In older children, symptoms such as dysuria, urinary frequency, and/or suprapubic discomfort are common with cystitis. These symptoms should prompt testing for UTI. However, when evaluating children for UTI, other diagnoses should be considered. Patients should be evaluated for non-UTI causes of dysuria, such as obstruction, *Candida* infection, and vulvovaginitis in female patients, by compiling a history and performing a physical examination. (11)

Dysuria and urinary symptoms, along with more systemic symptoms, such as flank pain, costovertebral pain, abdominal pain, and/or fever, are suggestive of upper urinary tract involvement and thus pyelonephritis. However, older children with UTI may present with systemic symptoms without dysuria or urinary symptoms. The differential diagnosis for symptoms of pyelonephritis includes appendicitis, viral gastroenteritis, bacterial enteritis, renal stones, and, in the female adolescent, pelvic infections.

DIAGNOSIS

Accurately diagnosing UTIs is critical. Establishing the diagnosis is important to be able to treat and resolve the infection with appropriate antibiotics, prevent further ascension of the infection to the kidneys, determine future risk of UTI, and avoid long-term renal disease. However, overtesting and overtreating expose children to painful procedures, unnecessary antibiotics, and worry. Therefore, careful assessment of the diagnostic test results is important.

The diagnosis of UTI in children is based on the results of urinalysis and urine culture. (6) Demonstration of both inflammation in the urine (WBCs, leukocyte esterase) and bacteria growing in the culture is critical. There are diseases that cause urinary inflammation without bacteria (sterile pyuria) in the urine. Examples include Kawasaki disease and infections outside the urinary system, such as viral infections or pneumonia. Also, bacteria may be present in the urinary tract without causing inflammation and infection (asymptomatic bacteriuria).

Compiling a history and performing a physical examination are important in establishing the diagnosis in all ages. Clinicians should screen for conditions that predispose the patient to or mimic UTIs, such as labial adhesions, *Candida* infection, and vulvovaginitis in female patients. In male patients, an obstructed urinary stream (such as dribbling of urine from the urethra) may suggest posterior urethral valves or phimosis.

Infants and Toddlers under 24 Months of Age

Urine Collection. Infants are generally not able to submit a clean-caught, voided specimen; therefore, catheterization is often performed to collect a urine sample for urinalysis and culture. Urine collection with a bag is also an option with special considerations, but the urine collected should only be analyzed for urinalysis and not culture. Bacteria growing on the skin in the genital area and not in the urinary tract could contaminate the bag specimen. When evaluating infants for UTIs, the clinician can review with the family the advantages and disadvantages of urine collection through catheterization or by using a bag, as reviewed in Table 2.

In 1 study, a pediatric emergency department was able to reduce the use of urinary catheterizations by one-half in infants and toddlers 6 months to 24 months of age, without missing UTIs by obtaining urine from bag specimens that were placed by the nurse early in the visit. (12) Patients with

TABLE 2. **Advantages and Disadvantages of Urine Collection via Bag versus Catheterization**

	ADVANTAGES	DISADVANTAGES
Catheterization	Quick Urine culture can be sent initially	Pain and discomfort
Bag specimen	May prevent the pain and discomfort from catheterization if urinalysis findings are normal	If urinalysis findings are abnormal (increased white blood cell count or leukocyte esterase) then would proceed to catheterization to confirm May take a substantial amount of time for an infant to void in the bag

bag urine specimens with evidence of inflammation (moderate or large leukocyte esterase or nitrites) underwent catheterization for culture and had antibiotics started while culture results were pending.

Suprapubic needle aspiration of urine from the bladder is also an option for obtaining urine specimens but is less commonly used because the procedure is more painful than catheterization and the success rate is low, being 53% in 1 study. (13)(14) A newer approach for urine collection in neonates and infants is the bladder stimulation technique first described in 2013. (15) The technique requires 3 trained providers and involves holding the infant upright while alternating between tapping the bladder and massaging the lower back. During this process, the third clinician waits, ready to collect the urine specimen midstream into a sterile container. Further studies are required to validate this technique before widespread use.

Interpretation of the Urinalysis Results. Once a urinalysis is obtained, the clinician must interpret the results carefully. Urine dipsticks can be used to analyze the presence of leukocyte esterase (a marker of WBCs) and nitrites (a marker of some gram-negative bacteria) among other things; however, urine dipsticks cannot be used to detect the concentration of WBCs. Microscopy of the urine allows WBC concentration data to be collected, which, together with leukocyte esterase and nitrite data, improve the sensitivity for UTIs, as shown in Table 3.

The nitrite test has poor sensitivity in infants because infants empty their bladders frequently, often before the 4 hours required for gram-negative bacteria to form nitrites. As such, absence of urinary nitrites does not rule out a UTI. However, with specificity of 98%, presence of nitrites is highly suggestive of UTI. Generally, 5 or more WBCs per high-power field or 25 WBCs per microliter is considered pyuria and increases the likelihood of UTI. (6)

Interpretation of the Urine Culture Results. Urine culture results also need to be carefully interpreted. The number of colony-forming units (CFUs) per milliliter, the number and types of species of bacteria identified, and the time elapsed in processing of the urine sample should all be considered. Generally, 50,000 CFU/mL and higher represents considerable urine bacterial growth and is clinically significant. (6) However, 10,000 to 50,000 CFU/mL may represent UTI, especially in neonates, children with immunodeficiency, children with urinary tract abnormalities, or children already taking antimicrobial therapy.

Even if a clinically significant amount of bacteria grows in the urine culture, this does not always represent UTI. Bacterial species, such as coagulase-negative staphylococci and *Corynebacterium*, are generally noninvasive in healthy children and could be contaminants or bacterial colonizers not causing infection.

Other Studies. Additional studies, such as blood culture and serum chemistry levels in infants suspected of having a UTI, are sometimes obtained in the initial workup of the fever. Assessing which infants with a UTI also have bacteremia is difficult and, in infants older than 2 months, is often not necessary, especially if the infant is well appearing. (16) The prevalence of bacteremia in infants less than 12 months of age with a UTI is about 4% and as high as 17% in infants less than 2 months of age. (16)(17)

Children 2 Years of Age and Older

Older children are more able to voluntarily submit a clean-caught voided urine specimen for analysis, making the need for catheterization or bag collection usually

TABLE 3. **Sensitivity and Specificity of Components on the Urinalysis, Alone and in Combination**

PARAMETER	SENSITIVITY (RANGE), %	SPECIFICITY (RANGE), %
Leukocyte esterase test	83 (67–94)	78 (64–92)
Nitrite test	53 (15–82)	98 (90–100)
Leukocyte esterase or nitrite test, positive findings	93 (90–100)	72 (58–91)
Microscopy, white blood cells	73 (32–100)	81 (45–98)
Microscopy, bacteria	81 (16–99)	83 (11–100)
Leukocyte esterase test, nitrite test, or microscopy, positive findings	99.8 (99–100)	70 (60–92)

From the AAP urinary tract infection guidelines. (6)

unnecessary. A clean-catch midstream void technique is recommended. (18)

Urinalysis and culture results should be interpreted similarly and carefully, as in infants. When interpreting the urinalysis results with clean-caught voided samples, clinicians should consider the number of squamous epithelial cells at microscopy. Squamous epithelial cells are predictive of a poor urine sample, and thus a poor performance of the urinalysis, because these cells suggest local genital skin contamination. (19) One should consider repeating the sample collection if there is a clinically significant concentration of squamous epithelial cells (5 cells per high-power field or higher). Sterile pyuria in older children may be caused by Kawasaki disease, non-UTIs, sexually transmitted infections, pelvic inflammatory disease, and appendicitis (if the inflamed appendix is close to the bladder).

Children with Neurogenic Bladder Dysfunction. Children with neurogenic bladder dysfunction deserve special consideration because these children are not able to empty the bladder normally and require clean, intermittent catheterization to prevent chronic renal disease, from both high urinary pressures and chronic UTIs. Examples include children with spina bifida and spinal cord injury. Children with neurogenic bladder dysfunction have a high prevalence of asymptomatic bacteriuria; therefore, the presence of bacteria at culture alone should not suggest a UTI. The definition of a UTI in this population has not been widely established, but most agree that all of the following should be established to assign a diagnosis: presence of symptoms (fever, pain, incontinence, or cloudy urine), inflammation at urinalysis, and clinically significant growth of a single bacterial species in the urine culture. (20)

MANAGEMENT

The care of children with UTIs requires consideration of the child's age, medical history, risk factors, degree of current illness, and other unique circumstances. Besides resolving the acute infection, management is important to prevent renal injury and subsequent long-term renal insufficiency.

Antibiotics

Many antibiotics, both oral and intravenous (IV), treat the bacteria responsible for UTIs. Oral antibiotics alone are as effective as IV antibiotics for UTIs, including pyelonephritis. (21)(22) However, IV antibiotics should be administered when a child is clinically toxic appearing and may also have bacteremia and/or sepsis or when the child cannot tolerate oral antibiotics. If IV antibiotics are warranted, the child should be transitioned to oral antibiotics when the clinical condition improves and when the patient can tolerate medications by mouth.

Culture results typically take 12 to 24 hours before bacterial growth is detected, 1 to 2 days before the specific bacterium is identified, and 2 to 3 days before susceptibilities are available. In infants and often in older children, antibiotics should be empirically initiated in suspected UTI after urinalysis but before culture results are interpreted to resolve the infection in a timely manner. However, in older children with mild symptoms, waiting for culture results can minimize unnecessary use or ineffective use of antibiotics.

The choice of the empirical antibiotic should be tailored to local bacterial susceptibility data, patient compliance, medication cost, and, if the patient has a history of prior UTI, the individual susceptibility pattern in prior infections. Antibiograms from local hospitals provide local susceptibility patterns of infectious organisms and are crucial because of varying geographic patterns. (6) See Table 4 for specific oral antibiotic choices. Table 5 depicts parental treatment options for UTIs.

A first-generation cephalosporin, like cephalexin, typically provides good coverage of uropathogens and is well tolerated, widely available, and cheap but must be taken at least 3 times per day. Trimethoprim-sulfamethoxazole is also tolerated well, is inexpensive, and requires twice-per-day dosing but has had increased resistance in past years

TABLE 4. **Some Empirical Antimicrobial Agents for Oral Treatment of UTI**

ANTIMICROBIAL AGENT	DOSAGE
Amoxicillin clavulanate	20–40 mg/kg per d in 3 doses
Sulfonamides	
Trimethoprim-sulfamethoxazole (should not be used in infants less than 2 mo of age)	6–12 mg/kg trimethoprim and 30–60 mg/kg sulfamethoxazole per d in 2 doses
Sulfisoxazole	120–150 mg/kg per d in 4 doses
Cephalosporins	
Cefixime	8 mg/kg per d in 1 dose
Cefpodoxime	10 mg/kg per d in 2 doses
Cefprozil	30 mg/kg per d in 2 doses
Cefuroxime axetil	20–30 mg/kg per d in 2 doses
Cephalexin	50–100 mg/kg per d in 4 doses

From the AAP urinary tract infection guidelines. (6)

TABLE 5. **Some Empirical Antimicrobial Agents for Parenteral Treatment of UTI**

ANTIMICROBIAL AGENT	DOSAGE
Ceftriaxone	50 mg/kg, every 24 h
Cefotaxime	150 mg/kg per d, divided every 6–8 h
Ceftazidime	100–150 mg/kg per d, divided every 8 h
Gentamicin	7.5 mg/kg per d, divided every 8 h
Tobramycin	5 mg/kg per d, divided every 8 h
Piperacillin	300 mg/kg per d, divided every 6–8 h

in some localities. Nitrofurantoin has good coverage of uropathogens but should not be used in pyelonephritis (and therefore younger children) because this drug does not penetrate renal tissue or blood well.

The duration of antibiotic therapy should depend on the age of the child and the degree of illness, such as lower versus upper tract involvement. For infants and toddlers less than 24 months of age or for older children with pyelonephritis, 7 to 14 days of antibiotics is recommended. (6) For older children with cystitis, a 3- to 7-day course may be adequate. Asymptomatic bacteriuria should not be treated except in pregnancy. Asymptomatic bacteriuria in pregnancy should be treated for 3 to 7 days. (23)

Imaging

Renal and bladder ultrasonography is recommended for infants and toddlers less than 24 months of age after a febrile UTI to detect anatomic abnormalities, such as an obstructive process. (6) The timing of the ultrasonographic examination depends on the clinical situation. Children who are very ill or who do not improve as expected (generally within 12–36 hours) should undergo ultrasonography within the first couple of days to assess them for an obstructive anatomic abnormality or renal abscess. Children with nonsevere infection can undergo ultrasonography after the acute phase of the infection has passed to reduce false-positive findings from renal inflammation 1 to 2 weeks later.

A voiding cystourethrogram (VCUG) should not be routinely performed in children after a first UTI. (6) A VCUG is used to evaluate the patient for vesicoureteral reflux (abnormal reflux of urine from the bladder into the ureters). Vesicoureteral reflux is graded from grade I (reflux into only the ureter) to grade V (clinically significant reflux to the kidney, with dilated ureters and calyces). Vesicoureteral reflux may predispose the child to upper urinary tract involvement and thus possible renal damage and, ultimately, long-term renal insufficiency. However, the cost, discomfort, and radiation from routine VCUGs after a first febrile UTI offset the potential benefit of identifying clinically relevant vesicoureteral reflux in every child with UTI. VCUG is, however, recommended in children less than 24 months of age who have had a febrile UTI and who had an abnormal renal and bladder ultrasonographic finding because these children are at higher risk of grade V vesicoureteral reflux.

Prophylaxis

Antibiotic prophylaxis with trimethoprim-sulfamethaxole for children with vesicoureteral reflux reduces the risk of UTI occurrence by one-half. (24) However, more than 5,500 doses of antibiotic are needed to prevent 1 UTI. (25) Antibiotic prophylaxis has not been shown to reduce renal scarring. (24) Twice-daily administration of an antibiotic may also lead to antibiotic resistance. The decision to routinely start antibiotic prophylaxis in children with vesicoureteral reflux remains controversial. When considering this option, the clinician should take into account each child's unique characteristics and involve the family in the decision. Children with grade V reflux have been excluded from most studies of this subject. These children should receive special attention and referral to a specialist, as most treat these children with antibiotic prophylaxis and sometimes surgical correction.

Prevention by Recognizing Bowel and Bladder Dysfunction

Preventing UTIs by screening for, identifying, and treating bowel and bladder dysfunction is not controversial and is underrecognized, effective, and safe. Inquiring about constipation symptoms, daytime wetting, and withholding behaviors will help identify children with bowel or bladder dysfunction. Bowel and bladder dysfunction occurs in 20% of all children and 50% of children with a history of UTI. (26) Constipation should be treated and managed. Among children with chronic constipation, 33% of girls and 3% of boys have UTIs. (27) One study showed that in children who had relief from their chronic constipation, UTIs were eliminated in those without anatomic abnormalities. (27) Bladder dysfunction can be treated by recommending scheduled voiding, such as every 3 to 4 hours, thereby preventing the child from voluntarily withholding urine until the last minute.

Children with a history of UTIs are at higher risk of developing subsequent UTIs than are healthy children. Families of these children should be educated to seek medical evaluation early for symptoms of a UTI—especially fever. (6)

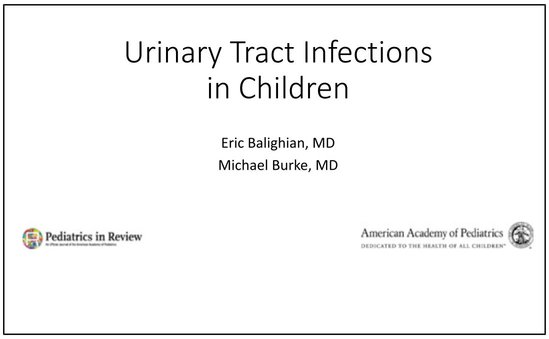
CASE STUDY CONTINUED

Thirteen-month-old Charlotte's risk factors for UTI include a febrile illness without a clear source, a history of prior UTIs, a temperature over or equal to 102.2°F (39°C), and fever duration of 2 days. She is definitely not considered low risk (≤2%) per the AAP UTI guidelines for infants and toddlers less than 24 months of age. A urine specimen should be collected to evaluate Charlotte for a UTI. She had urine collected from a bag that showed an increased WBC count and the presence of leukocyte esterase. The urine collected from a bag should not be sent for culture because of a substantial contamination rate; therefore, a catheterization should be performed to obtain a urine specimen for culture. Catheterization-obtained urine for culture and repeat urinalysis still demonstrated 5 to 10 WBCs per high-power field. The patient was started on cephalexin because local susceptibility patterns show that more than 90% of *E coli* are susceptible to this antibiotic. Charlotte's fever resolves in 2 days, and her culture result shows 50,000 CFU/mL of pan-sensitive *E coli*. After discussion with the family, it is decided to perform a VCUG to evaluate Charlotte for vesicoureteral reflux and, if present, administer possible antibiotic prophylaxis.

Summary

1. On the basis of strong research evidence, clinicians treating young children with fever without an apparent source should include UTI as part of the differential diagnosis. Clinicians should evaluate risk factors for UTI, including age, race, temperature, fever duration, and, in male patients, circumcision status.
2. On the basis of strong research evidence, young children with symptoms who are not low risk for UTI should undergo urinalysis. The urine specimen for urinalysis can be obtained via either bag or catheterization. Urine specimens obtained from bags can be helpful to rule out UTI if the results of the urinalysis are normal. However, if the urinalysis from the bag specimen has evidence of inflammation, catheterization is necessary for culture and repeat urinalysis. A culture should not be performed on a bag specimen.
3. On the basis of some research evidence, as well as consensus, the diagnosis of a UTI should include clinical symptoms, urinalysis with evidence of inflammation (leukocyte esterase and/or at least 5 WBCs per high-power field), and culture results of at least 50,000 CFU/mL of a typical uropathogen.
4. On the basis of strong research evidence, the choice of antibiotic therapy should take into account local susceptibility data, cost of the antibiotic, and patient compliance issues. Typical good choices, depending on local susceptibility, include cephalexin and trimethoprim-sulfamethoxazole. Trimethoprim-sulfamethoxazole should not be used in infants less than 2 months of age.
5. On the basis of some research evidence, as well as consensus, young children with a febrile UTI should undergo renal and bladder ultrasonography to rule out anatomic abnormalities or signs of obstruction. VCUG should not be performed routinely after the first febrile UTI.
6. On the basis of some research evidence, as well as consensus, clinicians should screen for and manage bowel and bladder dysfunction in older children. Appropriately managing bowel and bladder dysfunction reduces the development of UTIs.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/39/1/3.supplemental.**



Urinary Tract Infections
in Children

Eric Balighian, MD
Michael Burke, MD

Pediatrics in Review

American Academy of Pediatrics
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References for this article are at http://pedsinreview.aappublications.org/content/39/1/3.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition
- Chapter 344: Urinary Tract Infections - https://pediatriccare.solutions.aap.org/chapter.aspx?sectionId=125490707&bookId=1626

Point-of-Care Quick Reference
- Urinary Tract Infections - https://pediatriccare.solutions.aap.org/content.aspx?gbosid=165581

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1. A previously healthy 9-month-old African American uncircumcised male infant is brought to the clinic by his parents with a 12-hour history of fever. He has not had nasal congestion, cough, or diarrhea. He had 1 episode of emesis when he was given acetaminophen. He has continued to breastfeed and has had a normal number of wet diapers. His tympanic temperature is 101.1°F (38.4°C). He is mildly ill appearing. There is no discernible focus of infection on examination. Which of the following factors is most strongly associated with an increased probability for this infant having a urinary tract infection (UTI)?

   A. African American race.
   B. Duration of fever.
   C. Episode of vomiting.
   D. Temperature of 101.1°F (38.4°C).
   E. Being uncircumcised.

2. A previously healthy 6-month-old female infant is brought to the emergency department with a 2-day history of fever. She has not had vomiting, diarrhea, cough, or nasal congestion. There has been no known contact with ill persons. She has continued to breastfeed and has not had a decrease in the number wet diapers. Her temperature is 102.4°F (39.1°C). She is mildly ill appearing but alert and interactive. Examination shows no focus of infection. A bag urine sample is collected and sent for urinalysis. The urinalysis shows a specific gravity of 1.015, trace protein levels, 1+ leukocyte esterase result, positive nitrite result, and 10 to 12 white blood cells (WBCs) per high-power field. Which of the following results from her urinalysis has the highest specificity for having a UTI?

   A. Leukocyte esterase.
   B. Nitrite.
   C. Protein level.
   D. Specific gravity.
   E. WBC microscopy.

3. For the same 6-month-old female infant in question 2, a urine culture is performed via catheterization. After catheterization, she is noted to breastfeed normally. She is not allergic to any medications. Pending the urine culture result, which of the following is the most appropriate empirical therapy?

   A. Oral azithromycin.
   B. Oral cephalexin.
   C. Oral nitrofurantoin.
   D. Intravenous ceftriaxone.
   E. Intravenous cefepime.

4. A 4-month-old male infant presents with a 2-day history of fever. He is not vomiting and is alert and interactive. There is no focus of infection on examination. He is circumcised. A bladder catheterization is performed. The urinalysis shows a 2+ leukocyte esterase result, negative nitrite result, and 20 to 30 WBCs per high-power field. He has no allergies and is started on oral trimethoprim-sulfamethoxazole. The urine culture grows 50,000 colony-forming units (CFU) per milliliter of *Escherichia coli* that is susceptible to trimethoprim-sulfamethoxazole. After being sent home, his mother is called and states that he is acting well and has not had a fever in the past day. The mother is advised to have him complete the 10-day course of trimethoprim-sulfamethoxazole. Which of the following is the most appropriate next step in management?

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A. Dimercaptosuccinic acid renal scan.
B. No further testing or treatment indicated.
C. Renal and bladder ultrasonography.
D. Renal and bladder ultrasonography and voiding cystourethrogram.
E. Voiding cystourethrogram.

5. A 34-month-old girl is brought to the office with a 1-day history of dysuria and urinary urgency. She has not had a fever. She received a diagnosis of a febrile UTI at 20 months of age and had a normal renal bladder ultrasonographic finding. She had a second febrile UTI at 23 months of age, and a voiding cystourethrogram result was normal. She had a third UTI at 30 months of age and was afebrile. She has a history of chronic functional constipation with associated fecal incontinence. On examination, there is no costovertebral tenderness, and the vulvar area has some mild erythema. A clean-catch urinalysis is positive for leukocyte esterase and nitrite, with very few epithelial cells. The urine culture grows 100,000 CFU/mL of *Klebsiella oxytoca.* In addition to 7 days of antibiotic treatment, which of the following is the most appropriate next step in management?

A. Cefdinir prophylaxis.
B. Constipation management.
C. Cranberry juice daily.
D. Decreased dietary calcium intake.
E. Intravenous pyelogram.

Preparing Your Pediatric Patients and Their Families for the Operating Room: Reducing Fear of the Unknown

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Education Gaps

Clinicians should: identify the resources available to patients and families to allow for a smooth perioperative experience; understand the long-term effects and potential maladaptive changes associated with an anxiety-provoking perioperative period; understand the most common parental and patient concerns and misconceptions regarding surgery; understand the most common and up-to-date perioperative anesthesia practices; understand the indication for referral to the preoperative anesthesia clinic for patient evaluation to avoid unnecessary cancellation.

Practice Gap

Pediatricians are often tasked with preparing children and their families for the preoperative period and dealing with questions related to postoperative issues and concerns. Instruction based on current practice and new research and techniques may help patients and families cope with the stressors of surgery. Determining which patients may benefit from a medical or child life preoperative visit is of crucial importance.

Objectives

After completing this article, the reader should be able to:

1. Describe common preoperative anesthesia practice.
2. Recognize the role of a child life specialist in preparing children for surgery.
3. Differentiate children who would benefit from a preoperative anesthesia and/or child life evaluation.
4. Instruct patients and families on issues related to the perioperative period.
5. Address a wide array of parental concerns regarding surgery, anesthesia, and postoperative pain management.

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ABBREVIATIONS

BiPAP	bilevel positive airway pressure
CLS	child life specialist
CPAP	continuous positive airway pressure
DEA	Drug Enforcement Administration
IV	intravenous
MRI	magnetic resonance imaging
OSA	obstructive sleep apnea

INTRODUCTION

The period of time surrounding a planned surgical procedure can be tumultuous and anxiety provoking for both pediatric patients and their parents. The “mysterious place” that is the operating room often remains a mystery to many health care providers, including those tasked with caring for patients both before and after a procedure. As the health care provider most familiar to patients and their families, the pediatrician is in a unique position to allay many of the fears of a pending surgery, as well as initiate the perioperative preparation. This article provides a background for common pediatric operating room practices to refresh providers with the latest in pediatric perioperative care. The most commonly encountered parental and general concerns are presented as they relate to preoperative, intraoperative, and postoperative periods.

The perioperative period can be a highly intense and anxiety-provoking period for children and parents, with more than 60% of children experiencing anxiety during this period. (1) More than 50% of children undergoing general anesthesia and surgery exhibit negative behaviors (eg, regression of milestones, tantrums, bed-wetting) up to 2 weeks after the procedure. In 20% and 7% of children, respectively, these behaviors persist at 6 months and 1 year. (2) Additionally, the degree of anxiety expressed by parents is directly related to the anxiety levels noted in children. (3)(4) Numerous studies have demonstrated a direct correlation between a child’s perioperative anxiety and the incidence of postoperative emergence delirium, increased analgesic consumption, development of maladaptive behaviors, and a slower, more painful recovery. (5)(6)(7) Deliberate patient and parental preparation may help to minimize anxiety and prevent untoward perioperative issues. Parents who received more preoperative information and preparation report lower anxiety levels surrounding the event than those who were unprepared. (8)

PREOPERATIVE PARENT AND PATIENT CONCERNS

Parental Preoperative Concerns

Anesthesia practices vary dramatically between institutions. Certainly, it would be beneficial for pediatric providers to familiarize themselves with local practices, especially with respect to induction of anesthesia, allowing for the most accurate information based on regional practice. Tips and resources for surgical preparation are available in both English and Spanish to share with patients and families, free of charge. (9)(10)

Preparing Children for Surgery on the Basis of Age-Appropriate Fears and Misconceptions

A common question from parents is, “Should I prepare my child for surgery?” Children, when prepared for what to expect before hospital visits and procedures, cope better emotionally during the hospital visit. (11) Children between the ages of 1½ and 3 years develop a sense of autonomy and a desire to complete tasks independently and maintain some control over their environment. In the hospital setting, much of their control is taken away, causing many patients to react by protesting and being noncompliant. (12) Providing age-appropriate choices can enhance their experience and encourage compliance (eg, choosing a flavor for the anesthesia mask). Fortier et al demonstrated that children aged 7 to 17 years have a strong desire to receive perioperative preparation, especially with respect to postoperative pain management. (8) Children were noted to have less anxiety with preoperative preparation, including children who had undergone surgical procedures in the past. (8) A great deal of research on recognizing the benefits of reducing perioperative pediatric anxiety and stress has resulted in allocation of resources for perioperative emotional support, especially by child life specialists (CLSs).

CLSs and Preoperative Emotional Support Visits

CLSs are part of the multidisciplinary health care team and promote positive coping skills to help minimize stress and anxiety in the hospital setting through education, procedural preparation, and play-based therapeutic activities. CLSs are a resource provided free of charge by the hospital for patients and their families.

A CLS may be consulted to help provide developmentally appropriate preparation for surgery. CLSs use age-appropriate and specifically tailored preparation methods based on the child’s chronological and developmental age, anxiety levels, and prior hospital experiences. The medical procedure is described in terms of the child’s sensory experience (including all 5 senses) and sequence of events. Medical equipment may be used for demonstration while encouraging the child to handle and explore the equipment, promoting understanding, comfort, and familiarity, as well as an opportunity to demystify the encounter. Together with the parents, a plan is composed for effective coping strategies during the procedure. The CLS may also accompany the child to the operating room or procedure to provide a consistent and nonthreating presence.

Parents may choose to schedule an appointment with the child life department prior to the day of surgery. The CLS can provide appropriate information in advance to clarify many of the child’s misconceptions (Table 1). The CLS may also provide a tour of the surgical facility or procedural area (eg, the magnetic resonance imaging [MRI] room) to allay fear of the unknown for both child and parent. In some institutions, a mock operating room may be available to allow the child to simulate his or her role on the day of the

TABLE 1. **Age-Specific Preoperative Concerns and Suggestions for Child Preparation**

	AGE-APPROPRIATE CONCERNS AND FEARS	SUGGESTIONS FOR PREPARING THE CHILD FOR SURGERY
Infant	Infants cannot understand the reason for hospital visits or the reason for not eating or drinking	Bring comfort items.
	Infants may become fussy from hunger and thirst	Bring a blanket, pacifier, music, and other familiar items from home.
	The caregiver's anxiety can rub off on the infant	The caregiver should have an awareness of his or her own feelings and stress levels. Having emotional support on the day of surgery can be helpful.
Toddler	Hunger and thirst	Prepare the child 1 to 2 days before surgery.
	Separation from the caregiver	Use simple and general language to describe the sensory details (feel, touch, smell).
	Loss of control or autonomy	Remind the child that surgery is not punishment for "being bad."
	Fear of the unknown	
	Having the misconception that surgery is a punishment	
Preschool age	Hunger and thirst	Prepare the child 2 to 4 days before surgery.
	Separation from the caregiver	Use simple words without too many details; include sensory information.
	Fear of the unknown	Assure the child that the reason for the surgery is to get well and not because the child did anything wrong.
	Loss of control or autonomy	
	Having the misconception that surgery is a punishment	
School age	Fear of body mutilation, missing a limb	Prepare the child 1 to 2 weeks ahead of time.
	Pain	Be open to answering questions the child has, as best you can.
	Fear of deviation from routine	Explain what will happen before, during, and after the surgery; use minimally threatening sensory language (words like "cut," "incision," and "shot" are threatening).
	Fear of anesthesia or medicine, fear they will not wake up, fear they will wake up in the middle of a procedure	Never use threats or bribes ("If you don't hold still, the doctor will give you a shot").
		Encourage expression of fears and concerns.
Adolescent	Fear of scarring or altered appearance after surgery	Allow adolescents to hear about surgery from their physician.
	Fear of anesthesia, fear they will not wake up, fear they will wake up in the middle of a procedure	Facilitate choices and control; include them in the plan of care.
	Adolescents may not feel comfortable asking questions or saying they are scared	Respect autonomy and patient privacy.
	Fear of pain	Give the adolescent complete, honest explanations about surgery.
		Provide opportunities for your child to discuss concerns with staff.

procedure (Figure 1). After preparation, the CLS will encourage the child and family to ask questions and express feelings while determining if a formal plan for anxiety management is appropriate.

For children with anxiety beyond the normal range for their developmental level, the CLS can provide alternative interventions, such as distraction with play, watching a movie, listening to music, or involving the child in conversation to divert their attention from the hospital setting. Children with chronic illnesses and those requiring staged surgeries may benefit from an ongoing relationship with a particular CLS to provide consistency and continued strategies for anxiety reduction and coping.

Autistic Children

Hospital visits can be stressful for anyone, and this holds especially true for children with autism. Traversing the crowded facility and meeting a host of unfamiliar people can be particularly difficult and even traumatic for these children. For children with autism, the stress of going to the hospital is heightened because of their sensory sensitivities, speech and social deficits, and need for routine. In addition to the environmental sensitivities, not being able to eat or drink for a period of time can add to their stress levels.

Many hospitals provide services to adapt and modify the perioperative processes that help to minimize stressors or triggers for children with special needs, including autism. Parents should be instructed to communicate specific needs (eg, low-stimulation room) and past anesthetic experiences ahead of time to facilitate a smooth and uneventful perioperative experience. At many pediatric institutions, a parent questionnaire is administered to gather detailed information about the child's triggers, stressors, preferred ways of communicating, and preferred mode of comfort. By using this questionnaire, the multidisciplinary team can develop

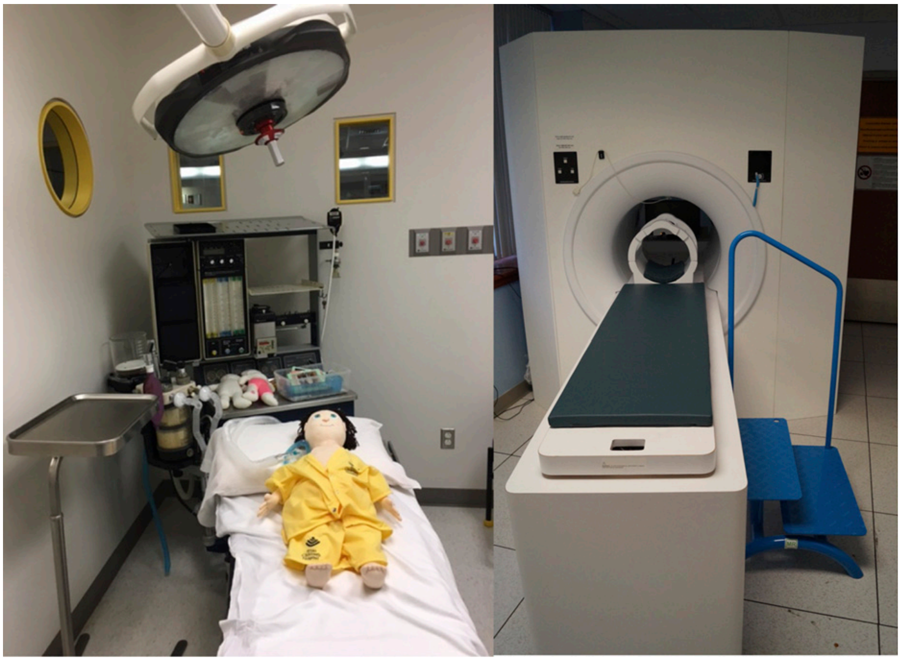

Figure 1. Viewing A. a mock operating room and B. the magnetic resonance imaging room provides children with the opportunity to interactively prepare for the day of their procedure and potentially reduce their anxiety levels.

a coping plan to customize the surgical process to the child's individualized needs. When appropriate, providers can instruct parents to contact the hospital, including child life and or anesthesia departments, prior to the day of surgery.

DISTRACTION TECHNIQUES AND AVOIDANCE OF GENERAL ANESTHESIA

For certain procedures (eg, MRI) and in patients who are appropriately cooperative, distraction techniques can be used, which obviate the need for general anesthesia. (13)(14) Distraction techniques have been used to mitigate procedural distress that may be associated with long-term maladaptive effects, including behavioral changes and emotional issues (eg, nightmares, separation anxiety, eating problems, and increased fear of physicians). Distraction is designed to shift attention from procedure-related pain and can be in the form of cognitive techniques (eg, counting, listening to music, non–procedure-related talk) or behavioral techniques (eg, breathing techniques, emotive imagery, reimagination of pain). (15) The theorized mechanism of action for distraction is based on the brain's limited immediate processing capacity to process stimuli and by "distracting" the brain (ie, with music). By doing so, there is reduced ability to focus on and process other stimuli, such as pain. Distraction for procedural relaxation is guided by the patient's emotional maturity, with younger children often responding better to task-oriented distractors (eg, use of interactive devices or video games), whereas older children can use breathing strategies and reimagination of pain.

A meta-analysis of distraction in children showed that the use of distraction techniques during painful procedures resulted in a significant decrease in self-reported pain and behavioral measures of distress. (16) Specifically, audiovisual distractors have proven successful in reducing distress for children who are undergoing painful procedures. (17)(18)(19) Active distraction strategies, such as music and engaging with interactive technologies, including tablet devices and video goggles, have been shown to decrease procedural distress and pain scores, all while increasing procedural tolerability. (20)(21)(22)(23) The choice of distraction method is based on the child's developmental age and cognitive ability, while considering the practicality of use for the specific procedure. (15) The plan for distraction and child preparation should be discussed with family and may be best performed with the assistance of a CLS. (13)

Since not all hospitals have readily available devices, parents may be instructed to bring these items on the day of surgery (eg, a tablet, gaming devices, or headphones). Use of these devices may also be helpful in distracting a child who does not understand the nil per os (nothing by mouth) guidelines. With the implementation of technological devices, such as video goggles, children can choose their own videos as a distraction during the MRI session (Figure 2).

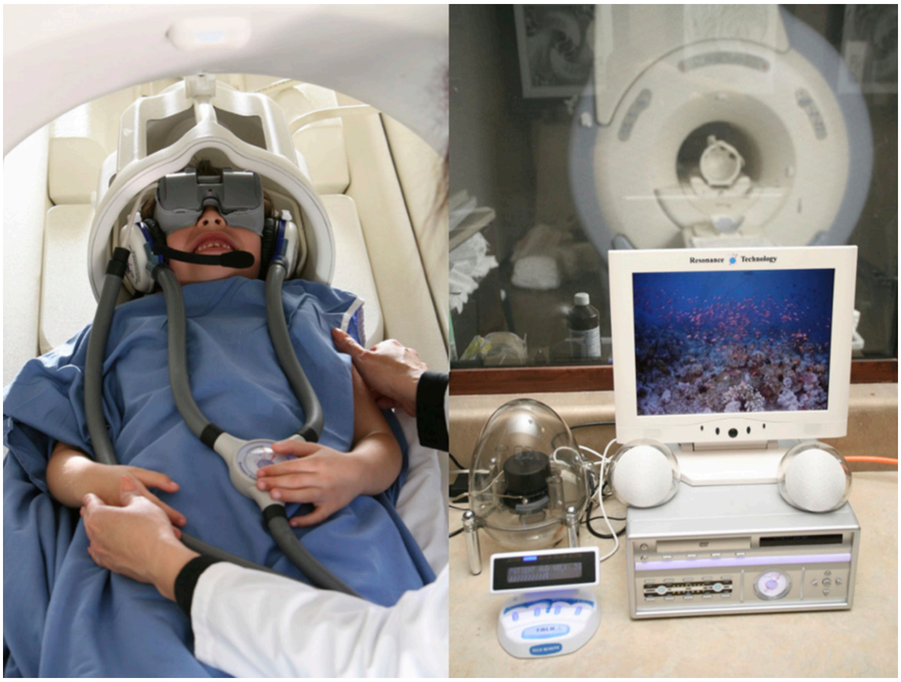

Figure 2. A. A child is using magnetic resonance imaging (MRI)–compatible video image goggles to watch movies during the imaging examination. The goggles are applied prior to entering the imaging unit to prevent claustrophobia. A microphone and earphones are worn to allow 2-way communication with the MRI technician and block noise from the imaging unit. The images were provided courtesy of Resonance Technology, Northridge, CA.

When assessing a child preoperatively or ordering an MRI, cooperative age and developmentally appropriate children should be considered for scheduling without anesthesia in centers in which this technology is used. Avoidance of anesthesia precludes the nil per os time, reduces distress related to anesthesia, and prevents the ill effects of pharmacological agents. One caveat to suggesting avoidance of anesthesia is for children who require MRI with contrast material, for which an intravenous (IV) catheter must be placed while the child is awake.

Preoperative Fasting Guidelines

The American Society of Anesthesiology has imposed strict nil per os guidelines for nonemergent cases that require general anesthesia, which serves as a great source of concern for parents preoperatively. Current nil per os guidelines can be found in Table 2. (24) Generally, younger patients are preferentially scheduled early in the day. To avoid dehydration, especially in young children, parents can be advised to provide clear liquids on the morning of surgery, 3 hours prior to their scheduled procedure. Children who are breastfed can be fed at a defined interval prior to their surgery or, alternatively, a solution that contains glucose (eg, Pedialyte; Abbott Laboratories, Abbott Park, Illinois) may be substituted. Numerous studies in adults have demonstrated the benefits of providing carbohydrate-rich drinks to patients preoperatively and showed consistently decreased anxiety,

TABLE 2. **Perioperative Fasting Guidelines from the American Society of Anesthesiology**

FOOD	NIL PER OS REQUIREMENT	EXAMPLE
Clear liquids	2 h	Apple juice, water (but no orange juice)
Breast milk	4 h	Unfortified
Infant formula	6 h	Unfortified
Non-human milk	6 h	Almond milk, soy milk, unfortified
Light meal	6 h	Tea and toast (no added fats or butter)
Full meal	8 h	Fatty meal

hunger, malaise, and thirst, without any evidence of increasing gastric volumes. (25) In situations of unforeseen delays, parents should serve as advocates and inquire about allowing clear liquids to be given. Avoidance of prolonged nil per os times has been associated with improved postoperative outcomes, decreased postoperative nausea and vomiting, reduced recovery stays, and greater patient satisfaction. (26) However, children with certain conditions (eg, polycythemia, sickle cell disease) may receive preoperative IV fluids or solutions that contain dextrose solutions, as indicated by their disease process.

Preoperative Clinic Visits

Aside from usual surgeon referral to the perioperative anesthesia clinic, a perioperative evaluation may be initiated by the pediatrician or the patient's family. The perioperative clinic assessment best allows for coordination of patient care and reduces the likelihood for procedure delays or cancellation on the day of surgery. Assessment of the patients' medical optimization prior to surgery is performed, as well as identification of the need for additional workup or subspecialty recommendations. Examples of situations where subspecialty recommendations would be indicated might include any organ system and could range from hemophilia to a metabolism plan for a patient with an underlying inborn error of metabolism. General conditions that require consideration for preoperative referrals to the perioperative anesthesia clinic are summarized in Table 3. The preoperative assessment aids in facilitating postoperative disposition planning and multispecialty care coordination. The perioperative clinic, in conjunction with the anesthesiologist, will indicate the appropriate venue for the surgical

TABLE 3. **General Conditions Requiring Consideration for Preoperative Medical Referrals to the Perioperative Anesthesia Clinic**

TYPE OF CONDITION	CONDITION OR CONSIDERATION
Respiratory diseases	Cystic fibrosis Oxygen, ventilator, CPAP, or BiPAP dependence Pulmonary hypertension Poorly controlled asthma
Airway anomalies	Complex airway malformations History of difficult airways or suspected of having difficult airways Complex craniofacial syndromes
Neuromuscular and orthopedic conditions	Muscular or mitochondrial dystrophies Cervical spine instability Uncontrolled epilepsy, ketogenic diets Vagus nerve stimulators
Hematologic conditions	Hemophilia, von Willebrand factor, and other factor disorders Thrombotic disorders Sickle cell anemia (not trait)
Metabolic conditions	Insulin-dependent diabetes End-stage renal disease, dialysis End-stage liver disease Major metabolic or genetic disorders
Posttransplantation state	Patient received heart, liver, or lung transplant
Ethical issues	Jehovah's witness Do-not-resuscitate order
History of anesthetic complications	Family history of anesthetic issues Malignant hyperthermia
Consent issues	Patients with complex consent issues Child protective services, intra-adoption, foster parents Avoiding same-day cancellation due to lack of consent
Parental or physician concerns	Autism Past concerns with anesthesia care Severe anxiety

BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure.

intervention (eg, the main operating room vs an outpatient surgical center). Inappropriate surgical site scheduling is an avoidable cause of day of surgery cancellation that may be prevented, given appropriate preoperative evaluation.

In addition, parents may request evaluation by the perioperative anesthesia clinic, especially in cases of past family or personal history of surgical or anesthesia-related complications. Patients with a family history of severe reactions to anesthesia (eg, malignant hyperthermia) and those with myopathies should also be considered for evaluation.

Not uncommonly, parents arrive on the day of surgery expecting additional procedures that are unanticipated and not previously scheduled (ie, "The neurologist said the next time my child has anesthesia, he should get an MRI"), which can result in dissatisfaction. The pediatrician and/or parent should communicate these needs or schedule a visit to the preoperative clinic so that arrangements for combined procedures may be facilitated in advance.

PREOPERATIVE UPPER RESPIRATORY TRACT INFECTIONS

Despite being one of the most common reasons for preoperative cancellation in children, guidelines for the management of perioperative upper respiratory infections are lacking. (27) The variability in practice for patients with upper respiratory infections stems from the heterogeneity in both patient symptoms and comfort level of the anesthesia provider. Elective surgical procedures are nearly universally cancelled for patients who are acutely ill. The gray area consists of patients with mild symptoms, especially those scheduled for potentially beneficial surgery (eg, ear tube placement for chronic otitis media or adenotonsillectomy for recurrent tonsillitis) and patients who are recovering from illness. Common considerations amongst anesthesiologists for determining procedure cancellation include temperature (>100.4°F [>38.0°C] and certainly >100.9°F [>38.3°C]), abnormal lower respiratory auscultation findings, productive cough, copious airway secretions, purulent mucus production, and reduced room air oxygen saturation. (28) Procedures scheduled at outpatient locations may influence the decision to proceed with surgery, as the ability to admit the patient postoperatively is not plausible. While an increase in overall respiratory adverse events in children with recent or active upper respiratory infections exists, the incidence of clinically significant respiratory complications is not greater and does not preclude anesthesia. (27)(28)(29) When in doubt, instruct the parent to contact the preoperative clinic or the surgeon's office directly (during business hours) or the anesthesia provider on call (if after hours via the hospital operator) to determine if the procedure should be preemptively cancelled to avoid unnecessary arrival at the hospital with a sick child.

Asthmatic Patients

Despite being one of the most common childhood illnesses, there are no formal consensus guidelines for the preoperative management of asthma. (30) While there is an increased risk of laryngospasm and bronchospasm with anesthesia in patients with reactive airway disease, it rarely precludes safe anesthetic administration. (31) In general, patients with moderate to severe asthma should be considered for a preoperative evaluation; recommendations from their managing provider should be obtained. Patients with more clinically significant asthma may not be appropriate candidates for surgery in the outpatient setting.

The general recommendation is for the patient to continue the medication regimen or advance 1 level on their asthma action plan. Those using β-agonists as needed are often instructed to use their inhalers daily for 2 days before surgery, on the morning of surgery, and continue after surgery as needed. (32) Patients should bring their inhalers on the day of surgery. Pulmonary function tests performed specifically for preoperative assessment are generally unnecessary. Patients with poorly controlled symptoms should be optimized prior to scheduling elective surgery.

Obstructive Sleep Apnea and Positive Airway Pressure

In general, obstructive sleep apnea (OSA) in children is multifactorial, with a greater incidence of non–obesity-related obstruction than in adults. Preoperative evaluation for children with severe OSA (most often due to adenotonsillar hypertrophy) is variable with respect to polysomnography. (33) While polysomnography is not indicated as a perioperative test, some ear, nose, and throat surgeons will obtain these data for help in postoperative disposition planning. Children with severe OSA are at high risk for postoperative apnea or hypopnea, which does not immediately improve with tonsillectomy. These children are often sensitive to opioids and other sedatives with respect to respiratory depression. Patients at high risk are often admitted for observation and continuous pulse oximetry. The criteria for determining the procedure location and postoperative disposition at The Children's Hospital of Philadelphia are highlighted as an example in Table 4; however, these criteria vary by institution.

With the increase in childhood obesity, many children are using home continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machines. Other

TABLE 4. **Criteria for Determination of Surgical Location and Postoperative Disposition in Children with Obstructive Sleep Apnea**

CRITERION	AMBULATORY SURGICAL CENTER	MAIN CAMPUS DAY SURGERY	MAIN HOSPITAL OPERATING ROOM WITH POSTOPERATIVE ADMISSION
Age and condition	≥3½ y, no comorbid conditions[a]	>3 y, no comorbid conditions[a]	All inpatients; all patients <3 y OR >3 y with any of the following conditions
Polysomnography results	AHI 0 to 10–23 and no high-risk gas exchange concerns (peak $EtCO_2 \leq 55$ mm Hg, O_2 nadir ≥ 90%)	AHI 0 to 10–23 and no high-risk gas exchange concerns (peak $EtCO_2 \leq 60$ mm Hg, O_2 nadir ≥ 85%)	AHI > 23 and high-risk gas exchange concerns (peak $EtCO_2 \geq 60$ mm Hg, O_2 nadir ≤ 85%)
Weight and related concerns	—	BMI < 30 (or BMI < 95th percentile), <3% failure to thrive	BMI > 35, <3% failure to thrive
Bed request	None	None	PICU or inpatient surgical unit

Data were obtained from the Children's Hospital of Philadelphia, per reference 60.

AHI=apnea-hypopnea index, BMI=body mass index, $EtCO_2$=end-tidal CO_2, PICU=pediatric intensive care unit.

[a] *Comorbid conditions include Down syndrome, craniofacial anomalies, neuromuscular disease (including cerebral palsy), chronic lung disease, sickle cell disease, metabolic disease, and BMI ≥ 95th percentile.*

indications for preoperative CPAP use include children with neuromuscular disorders and those with tracheostomies. Obtaining the patient's baseline CPAP or BiPAP settings is helpful in planning a perioperative ventilation plan, as are the results of the patient's previous polysomnogram, specifically the apnea-hypopnea index and saturation nadir. Generally, children with CPAP or BiPAP use should be considered for evaluation by the perioperative anesthesia clinic, as well as instructed to bring their home CPAP machine on the day of surgery. These patients are generally not appropriate candidates for procedures at the outpatient surgical center, as they are often kept overnight for monitoring. Regional anesthesia may be beneficial in select patients to decrease the opioid-induced respiratory depression.

Infective Endocarditis Prophylaxis

Indications for the administration of perioperative antibiotics, specifically for the prophylaxis of infective endocarditis, have changed dramatically over the past 20 years. (34) (35) Routine administration of antibiotics for genitourinary or gastrointestinal procedures is no longer recommended for the sole prevention of infective endocarditis. Additionally, antibiotic administration is recommended for patients deemed to be at high risk for the development of infective endocarditis (past endocarditis). Patients with congenital heart disease that required infective endocarditis prophylaxis should be considered for preprocedural evaluation by a cardiologist and/or the anesthesiology preoperative clinic.

Premedicants, Parental Presence, and Mask Induction

The method by which the pediatric patient is ushered into the operating room varies by institution. Induction of anesthesia is reported to be the most psychologically challenging time for the child during the perioperative period. (3) Children without IV access undergo induction of anesthesia by using inhalational gases. At some institutions, a parent (generally only one) is allowed to accompany their child to the operating room during the time of mask induction. While this process is not painful, parents should be informed that children often cry because of the unpleasant smell of the gas and their lack of control of the situation. Additionally, strange eye movements (nystagmus) and nonpurposeful limb movements are often observed, which, while expected, may be psychologically traumatic for parents. While favorable amongst parents, parental presence at induction has not been shown to alleviate anxiety in children. (36) Alternatively, patients may be given premedication, most commonly oral midazolam or IV midazolam, if IV access exists. A common misconception by parents is the thought that their child will be anesthetized prior to leaving them. While many children will become relaxed and even sleep, the goal of premedication, especially with midazolam, is to induce amnesia. Anxiolysis and amnesia are especially important for children who require multiple future interventions.

Use of premedication has been shown to be most effective at reducing patient anxiety when compared with parental presence and should be considered, especially in cases with highly anxious children or parents. (12) Premedication with midazolam has also been shown to reduce poor cooperation with induction of anesthesia, as well as appearance of postoperative behavioral changes. (12) In contrast, parental presence, while viewed positively amongst parents, has not been shown to be as beneficial for the child. (12)(37)

POSTOPERATIVE PARENTAL CONCERNS AND PATIENT ISSUES

Postoperative Overnight Admission

A common and avoidable "surprise" amongst parents for which they are unprepared is the required overnight stay for neonates after anesthesia. While institutional policies on postoperative discharge vary, there is generally a required overnight observational period where neonates are monitored for apnea after undergoing anesthesia. The basis for this is data from the meta-analysis by Coté et al, who demonstrated an increase in postoperative apnea in children on the basis of postconceptual age, as well as neonates with anemia (hematocrit level <30%). (38) At Texas Children's Hospital, term neonates younger than 4 weeks and preterm neonates younger than 52 weeks' postconceptual age are monitored overnight for apneic events. The monitoring period at The Children's Hospital of Philadelphia is extended until 60 weeks' postconceptual age.

Postoperative Nausea, Vomiting, and Hoarseness after Intubation

One of the most common anesthesia-related issues is postoperative nausea and vomiting, which serves as a substantial cause of patient dissatisfaction. Postoperative nausea and vomiting may last as long as 24 to 48 hours after surgery and may be exacerbated by the use of opioids postoperatively. Nausea and vomiting for durations longer than 48 hours after surgery should raise suspicion for other causes, including surgical and/or medication-related issues.

Commonly attributed risk factors include previous postoperative nausea and vomiting; motion sickness; ear, nose, and throat procedures; strabismus surgery; gastrointestinal and genitourinary procedures; age older than 3 years; female sex; dehydration; opioid use; and use of inhalation agents. (39) Concerned parents should alert their anesthesiology provider about a past history of postoperative nausea and vomiting so that prophylactic agents may be pre-emptively administered and/or triggering agents prophylactically avoided. (40) High-risk children can be instructed to consume clear liquids up to 2 hours prior to surgery. Prophylactic scopolamine patches, while infrequently used in pediatric patients, can be placed on the morning of surgery and may be appropriate for older children and adolescents.

A less frequently encountered postoperative concern is hoarseness. Most often, hoarseness is self-limited and caused by irritation of the vocal cords or surgical manipulation itself (eg, ear, nose, and throat procedures). In extremely rare cases, vocal cord or arytenoid cartilage damage has been reported after anesthesia. Injury to the recurrent laryngeal nerve during neck surgery (eg, thyroid surgery) and, more commonly, after cardiac surgery (eg, patent ductus arteriosus ligation) may result in hoarseness. Prolonged duration of hoarseness (>1–2 weeks) that does not abate with conservative treatment may necessitate a dynamic vocal cord evaluation by an otolaryngologist.

Postoperative Emergence Delirium, Milestone Regression, and Behavioral Changes

Postoperative emergence delirium is an anesthetic-induced phenomenon that can be potentially self-injurious to patients and traumatic for parents to observe. (41) The incidence of emergence delirium varies greatly in the literature on the basis of the criteria for diagnosis but occurs in approximately 12% to 18% of children and is related to the patients' age, the surgical procedure, and the anesthetic type. Emergence delirium occurs after exposure to inhalation agents (eg, sevoflurane) and manifests with uncontrolled and erratic behavior, flailing, and a state of delirium, at which time the child is dissociated from his or her surroundings. Emergence delirium is self-limiting; however, during the time of delirium, the patient is at risk for self-injury and disruption of IV lines, surgical drains, and dressings. (7) Emergence delirium is generally "treated" by allowing passage of a brief period of time, but administration of medications returning the patient to the hypnotic state (propofol, dexmedetomidine, midazolam) may be attempted. The occurrence of emergence delirium is likely to result in poor parental satisfaction with the perioperative experience. (42) Therefore, aside from treating the patient, it is important to address parental concerns after an episode of emergence delirium, as it can be traumatizing for a parent to witness. Providers should reassure parents that emergence delirium is self-limiting and a "normal" phenomenon that may occur after anesthesia and does not preclude the patient from receiving future anesthetic.

It is well known that after surgery, children may exhibit new-onset maladaptive behaviors and milestone regression. Described in up to 50% of children postoperatively, these behaviors include anxiety, enuresis, nighttime crying and/or night terrors, separation anxiety, and temper tantrums. (5) Increased levels of preoperative anxiety and presence of emergence delirium have been noted to increase the incidence of postoperative maladaptive behaviors. (3) Patients identified to be at risk for developing postoperative maladaptive behavior may be advised to request a premedication from the anesthesia provider to reduce preoperative anxiety.

Recurrent Anesthetic Exposure and Neurodevelopmental Issues

A major area of concern amongst parents is the question of neurodevelopmental effects of anesthesia drugs. With recent national media attention, parents frequently inquire about the effects of anesthesia on their young children. In December 2016, the United States Food and Drug Administration issued a warning against the prolonged and repeated use of anesthetics for longer than 3 hours in duration in children younger than 3 years of age. (43) Thankfully, while most anesthetics in children are far shorter in duration, this is certainly a concern shared by many parents and providers. At present, studies in animals are concerning for the development of neuroapoptosis after prolonged exposure to inhalation agents. Prospective neurocognitive development studies in children are ongoing, to attempt to conduct long-term neurodevelopmental analysis. Most studies, but not all, have thus far failed to solidify these findings in humans. Exposure to single and short-duration anesthetics prior to the age of 2 years did not demonstrate increased risk of learning disabilities. (44) A recently published landmark study on neurodevelopmental outcomes in anesthesia reported no evidence of adverse neurological outcomes by the age of 2 years after a single hour of anesthesia during infancy. (45) While it may be advisable to delay completely elective surgical procedures (eg, circumcision) until completion of these studies, most pediatric surgery that is longer than 3 hours in duration is medically necessary (eg, craniofacial and cardiac surgery). Single anesthetics of short duration in children under the age of 3 years has not been proven to result in long-term neurodevelopmental effects. Consensus statements regarding the safety of anesthetics in children are available for providers and parents from the SmartTots organization. (46) Certainly, pediatricians are in a unique position to discuss these concerns with parents and consider the potential risks of anesthetics when ordering certain tests. (47) Concerned parents should be advised to discuss this with the surgeon and/or contact the anesthesiology department prior to the day of surgery.

Pain Management after Discharge and Keeping the Child Comfortable and the Teenager Safe

A major concern of parents is safely administering opioids to their children after they leave the hospital. (48) Despite many pediatric patients experiencing moderate to severe pain after postsurgical discharge, there is substantial variability in the information provided to parents regarding analgesic dosing. (49)(50) While parents can generally assess their child's pain, there is lack of understanding regarding the effectiveness of analgesics, which often leads to undertreatment of pain. (11)(51)(52) Many parents report using less than the prescribed dose of opioids, switching to a less potent analgesic, or administering medication only for severe pain. (11)(50)(51)(52)(53) Untreated acute postoperative pain is a main risk factor in the development of chronic pain in children. (54)(55) Parents worry about side effects from opioids and the potential for addiction with exposure to these medications. (53) Opioids, which are given for a short duration and as prescribed, along with multimodal analgesia (eg, acetaminophen, ibuprofen) and nonpharmacological modalities where appropriate (eg, ice or heat, massage, distraction, relaxation) should adequately treat acute postsurgical pain. Additionally, this may help to prevent chronic pain and maladaptive pain syndromes and may aid in mobility and recovery postoperatively. In addition to the use of multimodal analgesia, improvements in postoperative pain management are also likely to occur with providing standardized written discharge instructions with respect to pain management and using surgery-specific pediatric analgesia guidelines when available. (56) When used appropriately in these settings, the concern for addiction postoperatively is extremely low. Persistent postsurgical pain, present despite treatment after an adequate time to allow for surgical healing (dependent on the surgical procedure and preoperative factors such as presurgical pain), should prompt evaluation by the surgeon. Untreated or inadequately managed pain may result in the development of behavioral and psychological consequences, as well as development of chronic pain. (53)(54) One opioid, however—codeine—is no longer recommended for use in children, especially after surgical procedures. (57) Evaluation of postoperative codeine-related fatalities has allowed identification of some patients to be "rapid metabolizers" of codeine. As dispensed, codeine is an inactive prodrug that requires metabolism to the active form, morphine. In some patients, genetic variability results in upregulation of cytochrome CYP2D6, which leads to a more rapid conversion of codeine to morphine, resulting in an effective overdose and the ensuing adverse effects (respiratory depression). (57)

Keeping children safe and comfortable at home is a challenge and concern of parents in the era of widespread addiction and abuse, especially given that the risks for prescription opioid abuse are highest in adolescents and young adults. (58) Aside from the risk to the patient, the presence of unsecured and unsupervised opioids in a home with teenagers places highly addictive and potentially deadly medications within reach of these at-risk adolescents. (58) Additionally, unused and unsecured prescription opioids could be fatal if ingested by toddlers or young children.

Evaluation of the epidemic of nonmedical use of prescription opioids has shown that many adolescents and young adults have used and/or abused prescription pain medications dispensed by medical providers (often prescribed for a family member or friend but also kept in the home because of medications being unused). (58) These unused (and unsecured or unsupervised) opioid medications that remain after surgical recovery pose a danger of accidental ingestion for very young patients and deliberate experimental ingestion in adolescents. Providers should instruct their patients and families about the safe disposal of these unused and unneeded medications. In 2010, the Drug Enforcement Administration (DEA) started a national drug "Take Back" campaign as a temporary means of collecting medications while legislative and regulatory action was being considered to develop more permanent and accessible disposal methods. DEA regulations allow registered law enforcement officials (eg, local law enforcement personnel) to take possession of and destroy controlled substances at any time. Whereas national "Take Back" days occur infrequently (biannually), permanent drug donation boxes serve as a means by which medications can be disposed of in a consistently accessible manner. Regional drop boxes are often available at police stations, and individual pediatrician offices should learn their locations. Additionally, mail-back programs are widely available, and materials can be purchased at local pharmacies or made available to patients in the office for a minimal fee (Figure 3). The DEA and the Food and Drug Administration have discouraged discarding unused or unneeded medications by flushing these down the toilet, as new and expanding evidence has demonstrated the environmental effects, specifically contamination of the water table. Patients and their families should be instructed not to flush or discard their medications but to call their local city or county government household trash and recycling service and ask if a drug take-back program is available in your community. Some counties hold household hazardous waste collection days, where prescription and over-the-counter drugs are accepted at a central location for proper disposal.

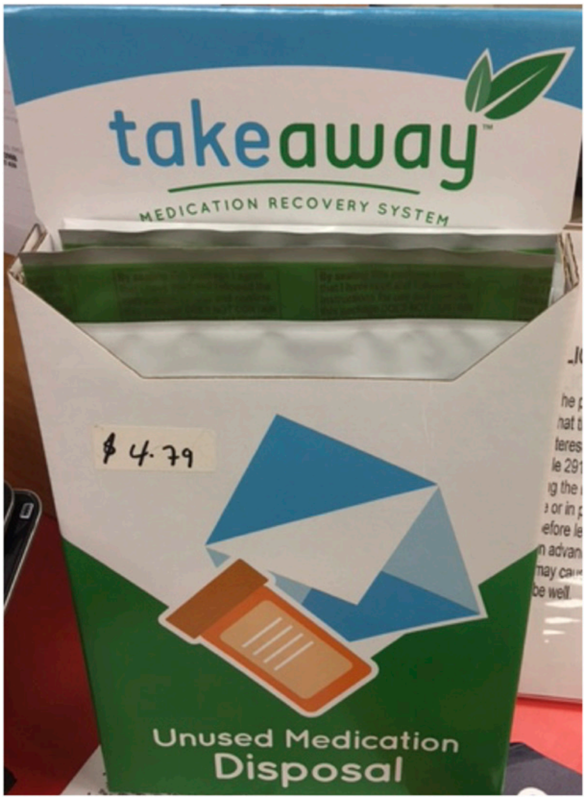

Figure 3. Example of a commercially available method for safe disposal of unused opioid medication (other brands available are MedReturn [http://www.medreturn.com/] and Dispose My Meds [http://disposemymeds.org/]).

If no hazardous waste collection program is available, the Environmental Protection Agency recommends the following steps for household drug disposal: *(a)* Take your prescription drugs out of their original containers. *(b)* Mix the drugs with an undesirable substance, such as cat litter or used coffee grounds. *(c)* Put the mixture into a disposable container with a lid, such as an empty margarine tub, or into a sealable bag. *(d)* Conceal or remove any personal information, including prescription number, on the empty containers by covering the information with a permanent marker or duct tape or by scratching it off. *(e)* The sealed container with the drug mixture and the empty drug containers can now be placed in the trash. Information sheets from the U.S. Environmental Protection Agency on safe and proper medication disposal are available for distribution to your patients. (59)

CONCLUSION

The perioperative period can be daunting for pediatric patients and families and can lead to anxiety and potentially maladaptive postoperative behavioral changes. Clinicians who can provide up-to-date and accurate information regarding perioperative issues from technical and emotional preparation to answering postoperative concerns may help allay these fears while addressing concerns appropriately.

SUMMARY

- Perioperative anxiolysis through preparation of both children and parents has been associated with better outcomes after surgery.
- On the basis of strong evidence, children who receive premedication prior to surgery have less anxiety and maladaptive behavioral issues postoperatively.
- Child life specialists (CLSs) are trained to help patients and families cope with the stress of surgery by using developmentally appropriate techniques.
- For children with medical or emotional concerns, a preoperative assessment may be scheduled with the anesthesiology preoperative clinic and/or with a CLS to develop a plan for the day of surgery.
- Distraction techniques such as video goggles can obviate the need for anesthesia in age-appropriate and developmentally appropriate children.
- Consumption of clear liquids may reduce the stress of fasting while reducing dehydration, hunger, and anxiety associated with nil per os times.
- Referral for preoperative anesthesia assessment can reduce the chance for day of surgery cancellation and improve coordination of care.
- While animal studies may suggest accelerated neuroapoptosis after anesthesia with inhaled agents, thus far, studies in humans have not definitively corroborated these findings.
- On the basis of strong evidence, treatment of postoperative pain is important in decreasing the risk of developing chronic pain issues.
- Proper disposal of unused opioids is crucial in preventing accidental or deliberate ingestion.

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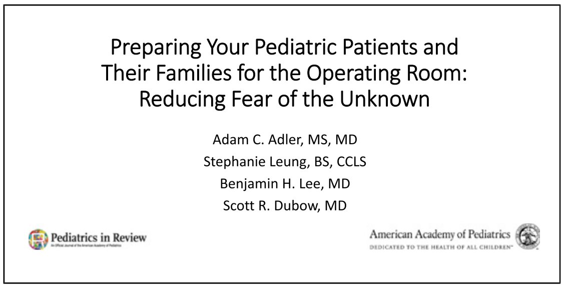

Preparing Your Pediatric Patients and
Their Families for the Operating Room:
Reducing Fear of the Unknown

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Pediatrics in Review

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1. The parents of a 9-year-old girl scheduled for eye surgery are very anxious about their daughter experiencing postanesthesia symptoms. As they have tried to prepare her for this surgery, she has become more anxious. Which of the following best describes the expected effect of perioperative anxiety in a patient of this age?
    A. Highly correlates with the amount of preoperative information provided to parents by the clinical team.
    B. Highly correlates with the amount of preoperative patient preparation provided by a child life specialist.
    C. Highly correlates with the degree of parental anxiety.
    D. No effect on analgesic requirements.
    E. No effect on the rates of emergence delirium.

2. A 6-year-old boy with a new diagnosis of acute lymphoblastic leukemia is scheduled for a long-term external catheter placement under general anesthesia tomorrow. As the anesthesiologist conducts a preoperative assessment, the parents are worried about the child being nil per os for a prolonged period of time for this nonemergent procedure, and they inquire about the minimum amount of time in which the child can have a full meal prior to the procedure. According to the American Society for Anesthesiology, which of the following is the minimum amount of time in which this child can have a full meal before his procedure?
    A. 24 hours.
    B. 16 hours.
    C. 12 hours.
    D. 8 hours.
    E. 4 hours.

3. A 4-year-old girl with severe asthma is scheduled for an elective orthopedic procedure. The parents are concerned and discuss with the operating physician whether any special considerations need to be given to her asthma prior to surgery. Which of the following is the most appropriate preoperative management recommendation in this patient, related to her asthma?
    A. Discontinue β-agonist use on the day of surgery.
    B. Obtain preoperative evaluation and recommendations from her managing pulmonologist.
    C. Perform pulmonary function tests, if not conducted within 1 year prior to surgery.
    D. Premedicate the patient with inhaled corticosteroid on the day of surgery.
    E. Reassure the family she can safely undergo her surgery in the outpatient setting.

4. Your hospital has implemented a new parent education program to improve the family and patient experience associated with surgical procedures. One of the aims of the education program is to inform parents about the most effective strategies to alleviate patient anxiety during the induction time. Which of the following strategies has been shown to be the most effective in addressing patient anxiety during induction of anesthesia in children?
    A. Parental presence.
    B. Placing the patient in 4-point restraints.
    C. The use of behavior modification and imagery.
    D. The use of inhalational gases for induction.
    E. The use of premedication.

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5. A 2-year-old boy is scheduled to undergo a bilateral hernia repair next week, to be performed under general anesthesia. The parents are concerned about the neurological and developmental effects of general anesthesia on their child. The patient is otherwise healthy, he was born full term, and he has never undergone general anesthesia before. Three months ago, he underwent laceration repair on his forehead by using local anesthesia. In addressing the parents' concerns, which of the following factors could potentially place this patient at the highest risk for neurodevelopmental effects of general anesthesia?

    A. Being full term.
    B. Having the first exposure to general anesthesia.
    C. Having the first exposure to premedication.
    D. Previous exposure to local anesthesia.
    E. Procedure duration longer than 3 hours.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Hyponatremia

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Knowledge Gaps

Hyponatremia is a common electrolyte disturbance in hospitalized children that is often related to increased action of antidiuretic hormone; practitioners should be familiar with clinical characteristics of children at risk for syndrome of inappropriate secretion of antidiuretic hormone (SIADH), as well as approach to diagnosis. By knowing how to identify children with SIADH or those at risk for developing hyponatremia, modifications can be made in the prescription of intravenous fluid to avoid the development of hyponatremia or to treat hyponatremia.

Objectives

After completing this article, readers should be able to:

1. Review the mechanisms that control water excretion and maintain normal plasma osmolality.
2. Describe the major causes of hyponatremia in children.
3. Apply clinical tests to identify children with hyponatremia to determine the underlying condition.
4. Identify children at risk for syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and modify fluid management to avoid development of hyponatremia.
5. Describe the approach to treatment of hyponatremia and, in particular, hyponatremia secondary to SIADH.

AUTHOR DISCLOSURE Dr Jones has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ADH	antidiuretic hormone
BUN	blood urea nitrogen
CNS	central nervous system
IV	intravenous
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
V2R	vasopressin 2 receptor

The discussion of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) begins with review of the causes of hyponatremia, since SIADH is a major cause of hyponatremia and hyponatremia is usually the abnormal finding that leads to its diagnosis. SIADH is defined as the presence of hypo-osmolality when urine is inappropriately concentrated (osmolality is inappropriately high) and there is no evidence of renal salt wasting or hypovolemia in an individual with normal renal, adrenal, thyroid, cardiac, and liver functions (Table 1). (1) It is reversible with water restriction. In SIADH, antidiuretic hormone (ADH) activity is considered "inappropriate," since there is no identifiable osmotic or hemodynamic stimulus for its action. Factors that control plasma osmolality and sodium levels, the major causes of hyponatremia in children and adolescents, how to evaluate the underlying cause of hyponatremia (including SIADH), how to identify children at risk, and how to approach the diagnosis and treatment of SIADH will be reviewed in this article.

PHYSIOLOGY OF OSMOTIC AND NONOSMOTIC CONTROL OF ADH SECRETION

Arginine vasopressin, also known as *ADH,* is produced by a subset of neurons in the paraventricular and supraoptic nuclei of the hypothalamus, the axons of which extend through the pituitary stalk into the posterior pituitary gland, where ADH is stored in granules. (2)(3) There are osmotic, hemodynamic, and nonhemodynamic or osmotic stimuli for ADH release. (4) The osmotic response for increased ADH secretion occurs with as little as 1% increase in plasma osmolality; the normal threshold is a plasma osmolality of 283 mOsm/kg (283 mmol/kg). Sensory neurons respond to changes in plasma osmolality with inversely proportional changes in cell volume; cells shrink in response to higher osmolality, activating the signaling cascade and resulting in vasopressin release. The thirst response is sensed by neurons in the ventromedial nucleus; thirst is activated at a higher plasma osmolality level than that which triggers ADH release—at 293 mOsm/kg (293 mmol/kg). The hemodynamic stimulation of ADH occurs when baroreceptors located in the carotid sinus, aortic arch, cardiac atria, and pulmonary venous system respond to decreased effective blood volume or blood pressure. The baroreceptor response is activated after a 5% to 10% decrease in effective blood volume. (2)(3)(5)

The increase in ADH release stimulates water reabsorption through binding to vasopressin 2 receptor (V2R) located on the basolateral (blood) membrane of the collecting duct principal cell; stimulation of V2R induces the movement of aquaporin water channels into the apical membrane. The physiological effect is to allow increased water entry from the lumen of the renal tubule, which results in reduced urine volume and increased urine osmolality. In the absence of ADH, such as when plasma osmolality level decreases below 280 mOsm/kg (280 mmol/kg), urine osmolality may reach less than 100 mOsm/kg (100 mmol/kg), which is the appropriate response to decreased plasma osmolality. However, as plasma osmolality increases to levels above normal, ADH increases free water absorption to lower plasma osmolality, ultimately achieving a urine concentration of approximately 1,200 mOsm/kg (1,200 mmol/kg). There are additional renal effects on sodium and urea transport that will not be discussed further in this review; readers are referred to references 2 and 6 for a detailed discussion. The hemodynamic stimuli for ADH will prevail over osmotic signals to suppress ADH production to restore extracellular volume. In addition, ADH levels may be increased by nonosmotic and nonhemodynamic stimuli, including conditions such as nausea, emesis, hypoxia, stress, pain, anesthesia, and numerous drugs (see Table 2).

Since sodium is the major determinant of plasma osmolality, hyponatremia is usually associated with hypo-osmolality. Solutes confined to the extracellular space, such as sodium and glucose, determine osmolality. The most common laboratory method for measurement of serum sodium level serves to determine the concentration in plasma and then enable calculation of the serum concentration. When there is an increase in the solid-phase components in plasma, such as hyperlipidemia or hyperproteinemia, the serum sodium concentration may be normal, but when measured in total plasma, the level appears low (due to displacement of the aqueous phase). (7) Measurement of plasma osmolality will confirm if hypo-osmolality is truly present. Alternatively, excessive extracellular solutes, such as glucose and mannitol, may increase the plasma osmolality level and cause hyponatremia in the absence of hypo-osmolality. When there is excess solute to which the cell membrane is relatively impermeable, then water moves according to the osmotic gradient from the intracellular space to the extracellular space, resulting in decreased sodium concentration but normal to increased plasma osmolality levels.

TABLE 1. Definition of Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Definition of syndrome of inappropriate antidiuretic hormone secretion:
• Hypotonicity and hyponatremia (plasma osmolality <280 mOsm/kg, plasma sodium < 135 mEq/L)
• Inappropriately concentrated urine (urine osmolality >100 mOsm/kg)
• High urine sodium concentration (>20 mEq/L, except during sodium restriction)
• Absence of sodium excess (edema) or clinical signs of volume depletion
• Normal renal, cardiac, hepatic, adrenal, and thyroid function

To convert milliosmoles per kilogram to millimoles per kilogram, multiply by 1. To convert milliequivalents per liter to millimoles per liter, multiply by 1.

TABLE 2. Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone in Children

ACUTE CONDITIONS	PULMONARY DISEASE	NEUROLOGICAL DISEASES	MEDICATIONS	MALIGNANT DISEASE	HEREDITARY CAUSES
General anesthesia	Positive pressure ventilation	Meningitis, encephalitis	Carbamazepine	Lymphoma	Gain of function mutation V2R
Stress	Bronchiolitis	Tumors	Vincristine	Ewing sarcoma	
Nausea	Pneumonia	Trauma	Cyclophosphamide	Carcinoma (lung, bladder, etc)	
Pain	Asthma	Hydrocephalus	Tricyclic antidepressants		
Stress	Cystic fibrosis	Brain abscess	Narcotics		
		Rocky mountain spotted fever	NSAIDs		
		Cavernous sinus thrombosis	MDMA (ecstasy)		
		Guillain-Barré syndrome	SSRI		
		Cerebrovascular accident	Desmopressin		
		Subdural hematoma	Ciprofloxacin		
			Amiodarone		

For a complete list, see references 1 and 2.
MDMA=3,4-methylenedioxymethamphetmine, NSAIDs=nonsteroidal anti-inflammatory drugs, SSRI=selective serotonin reuptake inhibitor; V2R=vasopressin 2 receptor.

DIAGNOSIS OF SIADH AND OTHER HYPONATREMIC DISORDERS

Although the definition of clinically significant hyponatremia has evolved, currently it is defined as the presence of serum sodium level less than 135 mEq/L (135 mmol/L); it is the most common electrolyte disturbance among hospitalized adults, with an estimated incidence of 15% to 30%. Hospital-acquired or iatrogenic hyponatremia has been reported to account for 40% to 75% of all cases of hyponatremia among adults. Certain groups are at increased risk for hyponatremia, including adults with heart failure, adults with cirrhosis, and elderly adults residing in chronic care facilities (related to excess water from tube feedings or flushes and underlying central nervous system [CNS] disease). (8) Hyponatremia can increase the risk for morbidity and mortality among adults; hyponatremia is considered to represent a surrogate marker of overall neurohormonal activation, particularly of the renin-angiotensin system.

The incidence of hyponatremia among hospitalized children has been reported to be 1.4% to 45%, depending on the definition (<130 mmol/L or <135 mmol/L) and whether hyponatremia was present at initial evaluation or developed after administration of intravenous (IV) fluids. (4) Incidence of patients with sodium level less than 135 mEq/L (135 mmol/L) at admission ranged from 17% to 45% (9)(10)(11), while patients with more severe hyponatremia (<130 mEq/L [<130 mmol/L]) comprised 3.7% of admissions (11); hospital-acquired hyponatremia (<135 mEq/L [<135 mmol/L]) occurred in 20% to 35% of patients, (10)(12)(13) while 1.4% to 5% of patients had sodium levels less than 130 mEq/L (130 mmol/L). (12)(14) Hyponatremia can be classified as that related to the acute illness (present at initial evaluation) or hospital acquired (or iatrogenic). Among children hospitalized at Texas Children's Hospital over 12 months, at admission, 161 of 11,702 patients (1.4%) had a serum sodium level less than 130 mEq/L (130 mmol/L). (14) Of these, 43% had hyponatremia at admission, and 57% developed hospital-acquired hyponatremia. This level of hyponatremia would be defined as moderate to severe by current standards. Most children (77%) with hyponatremia had some form of chronic medical condition. The most common etiologic origins identified were gastroenteritis, which was the most common cause at admission, and diuretics, which were the most common cause of hospital-acquired hyponatremia. Other common causes were SIADH, nasogastric or chest tube fluid loss, and hyperglycemia. (14) The incidence of hyponatremia (sodium level <135 mmol/L) in children with community-acquired pneumonia was 45%; moderate (sodium level < 130 mmol/L) to severe (sodium level <125 mmol/L) hyponatremia was present in 3.7%. (11) The prevalence of hyponatremia at admission to the pediatric intensive care unit was 33% in a prospective, randomized, single-center cohort study also designed to evaluate the effect of hypotonic versus isotonic fluids on serial serum sodium levels. (15) In another study designed to analyze risk factors for development of hyponatremia after administration of IV fluid, 22% of children in whom at least

2 sodium levels were measured had hyponatremia (sodium level < 130 mmol/L). Of those with hyponatremia, 64% had hyponatremia at baseline assessment. Some patients who initially presented with hyponatremia had hyponatremia reoccur: A total of 9% (40 of 432) developed hyponatremia during hospitalization, with decrease in mean serum sodium level ± SD from 139 ± 3 mEq/L (139 ± 3 mmol/L) to 133 ± 3 mEq/L (133 ± 3 mmol/L). (10) Children with iatrogenic hyponatremia were more likely to exhibit nausea and vomiting, to have postoperative status, and to have received a greater volume of electrolyte-free water (further discussion to follow). Morbidity and mortality related to hyponatremia have been reported in children, particularly those who receive anesthesia or are in the postoperative state. Since many children undergoing surgical procedures do not have serum electrolyte levels measured prior to surgery, the incidence of hyponatremia, particularly baseline hyponatremia, may be underestimated; only 6% of patients enrolled in a prospective, randomized study of a pediatric surgical cohort had baseline serum sodium levels measured. (16)

CLINICAL SIGNS AND SYMPTOMS OF HYPONATREMIA

Symptoms of hyponatremia are nonspecific and include headache, nausea, vomiting, muscle cramps, lethargy, restlessness, confusion, and seizures. Rapid change in serum sodium concentration is associated with acute neurological compromise. The major physiological effect of hyponatremia is neurological dysfunction related to cerebral edema, a condition known as *hyponatremic encephalopathy*. Because of the inability of sodium to cross the blood-brain barrier, hyponatremic encephalopathy is the result of cerebral cell swelling caused by water movement into the cell to establish equal osmolality between the extracellular and intracellular spaces. Regulatory mechanisms to restore cell volume toward baseline include efflux of electrolytes and reduction of cell volume. Slower adaptation occurs with generation of organic osmolytes that can be released to maintain cell volume toward normal. If plasma tonicity rapidly increases, brain cells, which contain a lower-than-normal quantity of osmolytes, will respond by decreasing cell volume as water moves from the intracellular to the extracellular space. Thus, rapid correction of hyponatremia may potentially lead to additional neurological sequelae, known as *pontine myelinolysis*, which is characterized by demyelination of pontine and extrapontine neurons (osmotic demyelination); clinically, this may manifest as seizures, coma, paralysis, and death. (7) Osmotic demyelination is extremely rare in children. The reader is referred to reference 4 for an excellent review of hyponatremic encephalopathy in children.

Most reviews on the subject of hyponatremia focus on adults and provide exhaustive lists of potential causes, while there is a paucity of information on the epidemiology of hyponatremia in children. Much of the current literature addresses how best to approach the prescription of IV fluid therapy in hospitalized children at risk for SIADH in an effort to avoid the development of hyponatremia (to be covered in the following sections). In general, hyponatremia is caused by solute loss (sodium deficiency) or water excess (water retention in excess of sodium retention). (1)(2)(17)

The classic diagnostic approach to determine whether hypo-osmolality or true hyponatremia is present is via measurement of the plasma osmolality. If hypo-osmolality is confirmed, the etiologic origin of hyponatremia can be classified into 3 major categories on the basis of the extracellular fluid volume: decreased, normal, or increased (Fig). Further classification depends on the urinary sodium excretion.

Causes of hypovolemic hyponatremia can be classified into renal and extrarenal sodium loss. Among children, the most common causes include *(a)* gastrointestinal losses of fluid and electrolytes from gastroenteritis and acute intra-abdominal processes, such as nasogastric suction, ostomies, and fistulas; *(b)* renal losses from salt-wasting nephropathies, osmotic diuresis, diuretic medications, or adrenal insufficiency; *(c)* skin loss from burns and, rarely, cystic fibrosis; and *(d)* conditions associated with third-space sequestration, such as sepsis and anaphylaxis. Urinary sodium concentration and excretion can be used to differentiate between primary salt-wasting disorders and conditions with nonrenal loss. When hypo-osmolality occurs in the setting of hypovolemia or reduced effective plasma volume (third-spacing), the nonosmotic stimulus for ADH secretion will override the osmotic signals and result in higher-than-appropriate urine osmolality. Repletion of the vascular volume with isotonic fluid would be expected to reverse the process and result in an ability to excrete a dilute urine and normalization of serum sodium concentration. Factors that help to differentiate hypovolemic hyponatremia from hyponatremia with normal or increased extracellular fluid volume include a history of fluid loss and/or decreased oral intake, increase in heart rate or decrease in blood pressure, orthostatic change in blood pressure or heart rate, increased blood urea nitrogen (BUN) or BUN/creatinine level, and increased serum uric acid level. Provision of isotonic fluid will correct hyponatremia in this setting.

Causes of hyponatremia with normal extracellular fluid volume include SIADH as the major cause, with glucocorticoid and hypothyroidism as minor causes. In most cases of SIADH, urinary sodium level is high, greater than 20 mEq/L (20 mmol/L); however, in cases of poor oral intake

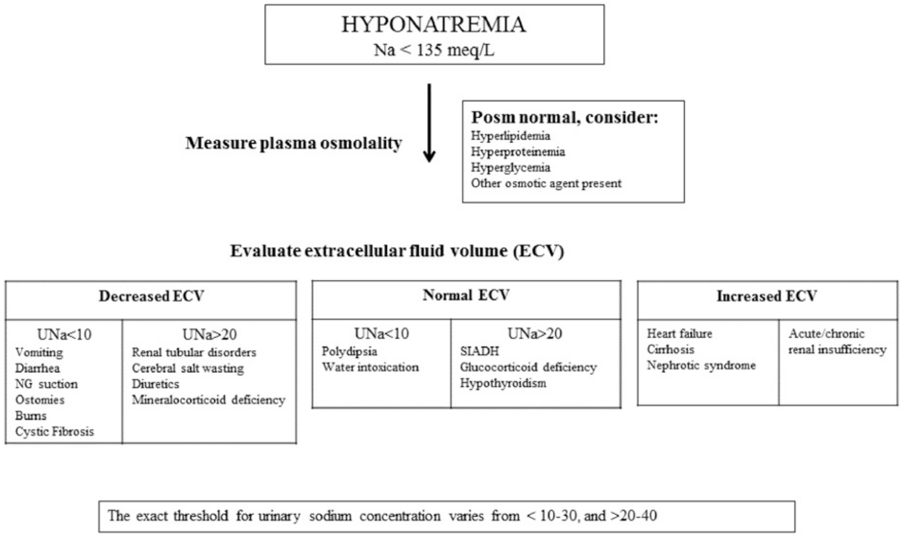

Figure. Proposed approach to the diagnostic evaluation of hyponatremia. Initially confirm that the patient has hypo-osmotic hyponatremia by measuring the plasma osmolality. If the patient has hypo-osmotic hyponatremia, then evaluate volume status and urinary sodium excretion. ECV=extracellular fluid volume, NG=nasogastric, Posm=plasma osmolality, SIADH=syndrome of inappropriate secretion of antidiuretic hormone, UNa=urine sodium.

or low sodium intake, the urinary sodium levels in individuals with SIADH may be low. Low BUN and uric levels support SIADH as the underlying diagnosis. Approach to the treatment of SIADH will be discussed in the section below. Hyponatremia secondary to polydipsia is rare in children; however, urine osmolality level less than 100 mmol/kg should raise concern about the possibility of water intoxication (such as improper feeding of an infant or near-drowning).

In conditions in which the effective plasma volume is low, the nonosmotic stimulus for ADH secretion will override the osmotic stimulus, leading to total-body sodium overload with excess of water. Major causes of hyponatremia with extracellular fluid volume excess include nephrotic syndrome, congestive heart failure, kidney failure, and cirrhosis. Approach to correction of these disorders often includes fluid restriction and diuretics.

When serum sodium level is found to be lower than normal (<135 mEq/L [<135 mmol/L]), repeating measurement of serum electrolyte levels, BUN levels, glucose levels, and plasma osmolality levels is advised to rule out sampling or measurement error and to assess the patient for pseudohyponatremia and hyperglycemia. Urine osmolality, potassium, and sodium levels should also be obtained to assist with the diagnostic evaluation of the underlying cause and to assist with planned correction. Other helpful tests include serum uric acid level, which is high in hypovolemia and normal to low in SIADH.

For symptomatic patients with hyponatremia, a modest increase in the serum sodium level is recommended via administration of 3% saline, 2 mL/kg delivered as a bolus with maximum volume of 100 mL. (4) This can be repeated if neurological symptoms persist. Overall correction of hyponatremia should occur slowly to prevent osmotic demyelination—no faster than 8 to 10 mEq/L (8–10 mmol/L) over the first 24 hours and no more than 18 to 25 mEq/L (18–25 mmol/L) over the first 48 hours. Tolerance to correction will depend on the duration of hyponatremia, since the compensatory mechanisms of the central nervous system will be more established with chronic hyponatremia. Chronic hyponatremia requires more gradual correction than acute hyponatremia to avoid CNS complications, so the current guidelines recommend the goal of 10 mEq/L (10 mmol/L) per 24 hours for acute hyponatremia and 6 to 8 mEq/L (6–8 mmol/L) per 24 hours for chronic hyponatremia. (18)

Formulas used to estimate the effect of the sodium concentration of IV fluids used for correction of hyponatremia on the serum sodium level are available; (1) however, they may actually lead to underestimation of the rate of increase in serum sodium level in some patients. One reason for the inaccuracy of these formulas is that there may be escape from the ADH effect once hypovolemia has been corrected. (2) This escape from ADH effect would be accompanied by greater ability to dilute the urine due to increased free water excretion, resulting in a more rapid increase in the serum sodium level. The formula proposed by Adrogué and Madias (7) was formally tested in adults with hyponatremia. (19) The predicted sodium concentration tended to be slightly lower than the actual sodium concentration at 12, 24, and 36 hours; however, in individuals with hypovolemia due to extracellular volume depletion, the predicted sodium concentration at 24 hours was 5 to 6 mEq/L (5–6 mmol/L) lower than the actual sodium concentration. Therefore, no formula is consistently accurate in predicting the rate of increase of the serum sodium level. Careful monitoring of electrolyte levels and fluid balance is required to avoid overly rapid correction.

TRUE SIADH AND HYPONATREMIA SECONDARY TO APPROPRIATE BUT NONOSMOTIC CONTROL OF ADH SECRETION

When the plasma osmolality is less than 275 mOsm/kg (275 mmol/kg), the normal renal response is to excrete a dilute urine so that urine osmolality should be approximately 100 mOsm/kg (100 mmol/kg). Therefore, if the urine is more concentrated than 100 mOsm/kg (100 mmol/kg) when the plasma osmolality is less than 275 mOsm/kg (275 mmol/kg), a nonosmotic stimulus for ADH or inappropriate secretion of ADH must be present. Such nonosmotic stimuli include low effective plasma volume or nonhemodynamic or nonosmotic stimuli, such as pain, nausea, stress, and numerous pharmacological agents and disease states (see the following discussion).

Four mechanisms have been described for the actions of vasopressin during hypo-osmolality: nonosmotic release induced by stimuli from the paraventricular or supraoptic nuclei, ectopic production, factors that enhance the renal effects of vasopressin, and an activating mutation of the vasopressin receptor. (2) The presence of inappropriately concentrated urine (>100 mOsm/kg [>100 mmol/kg]) in a child with true hyponatremia indicates that a nonosmotic stimulus for ADH is present, such as a hemodynamic stimulus or a nonosmotic or hemodynamic stimulus. One should suspect that SIADH is present in acute care settings known to increase the risk for nonosmotic release or actions of ADH, such as children with pain, nausea or vomiting, postanesthetic status, or pulmonary or CNS disease (see Table 2). In these children, SIADH is an acute condition that is suspected to resolve. Chronic hyponatremia due to SIADH is not common in children but may occur in children with chronic CNS or pulmonary conditions. The nephrogenic syndrome of inappropriate antidiuresis is a rare disorder described in children who have the clinical picture of SIADH but have no detectable circulating ADH. The reported cases of this syndrome are the result of a gain of function mutation in V2R. This mutation results in sustained generation of cyclic adenosine monophosphate, which leads to insertion of more water channels on the apical surface of the collecting duct, resulting in increased water reabsorption and hyponatremia. (20)(21)

Treatment of SIADH should start with prevention. Recognition of children at risk can allow tailored IV or fluid therapy and more careful monitoring. Once SIADH is present, therapy includes *(a)* identification and treatment of the underlying cause and *(b)* measures to gradually correct the serum sodium level toward normal values at a safe rate. The major causes of SIADH (modified to those more likely to occur in children) are listed in Table 2.

The first-line treatment of SIADH is fluid restriction, although there are no clear guidelines regarding the exact amount of fluid restriction required. Alternative therapies include *(a)* furosemide and sodium supplementation, *(b)* urea administration, and *(c)* vasopressin receptor antagonist administration. Demeclocycline and lithium, agents for which the side effects include nephrogenic diabetes insipidus, have been used to treat chronic SIADH in the past but are no longer drugs of choice. The use of furosemide to treat hyponatremia related to SIADH seems counterintuitive; however, loop diuretics inhibit free water absorption, which overrides their effect of increasing sodium and potassium excretion; however, supplemental sodium chloride and/or potassium chloride may be required to avoid negative sodium or potassium balance. (22) Urea supplementation is also used to treat chronic SIADH by increasing the excretion of electrolyte-free water. As an osmotic agent, urea increases water excretion by inducing an osmotic diuresis and is also associated with a decrease in urinary sodium excretion in patients with SIADH. (23) The recommended starting dose is 0.1 g/kg per day, divided into 4 doses, with a maximum dose of 2 g/kg per day. (24) Urea had equivalent effectiveness and tolerance in adults with SIADH, as compared to vaptans (see the following discussion). (23)

A class of drugs known as *vaptans* shows promise for treatment of chronic hyponatremia, including SIADH. Vaptans inhibit the vasopressin receptor, resulting in increased free water excretion, or aquaresis. Conivaptan inhibits both V1a and V2 receptors and is available only in IV form, whereas tolvaptan is a specific antagonist of V2R and is available in oral form. Vaptans have been successfully used to treat hyponatremia in adults with SIADH and hyponatremia from other etiologic origins, such as congestive heart failure, and was approved by the Food and Drug Administration in 2009 for treatment of euvolemic and hypervolemic hyponatremia. Studies in adults with hyponatremia (including SIADH) indicate that both conivaptan and tolvaptan are effective in the correction of hyponatremia and are well tolerated. Common effects associated with vaptans include increased thirst and dry mouth due to increased urine volume. (25)(26) Reports of the use of vaptans in children are limited. Continuous conivaptan infusion (20–30 mg per 24 hours) was used to treat refractory hyponatremia secondary to SIADH in a 13-year-old with large cell lymphoma to allow aggressive hydration for induction chemotherapy. (27) Intermittent bolus IV conivaptan (0.15 mg/kg) was used to treat SIADH in a

19-month-old with traumatic brain injury. (28) Tolvaptan was used to treat hyponatremia in 2 infants with SIADH by using doses of 0.1 to 0.6 mg/kg per day by crushing the tablets and mixing them with water. (29) Two additional case reports indicate successful treatment of fluid overload secondary to congestive heart failure with tolvaptan (0.1 mg/kg per day). (30)(31)

For symptomatic hyponatremia in children, Moritz and Ayus recommend the administration of 3% NaCl in children with a suspected hyponatremic encephalopathy: 2 mL/kg with a maximum of 100 mL, which can be repeated as needed until CNS symptoms improve. (4)

IV FLUID THERAPY IN HOSPITALIZED PEDIATRIC PATIENTS

Hospitalized children are at increased risk for hyponatremia secondary to SIADH because of the presence of conditions that stimulate ADH release by nonosmotic and nonhemodynamic stimuli. (32) Conditions associated with increased ADH release include nausea, stress, pain, surgery, and certain medications, as well as pulmonary and CNS diseases commonly seen among hospitalized children, such as pneumonia, bronchiolitis, asthma, positive pressure ventilation, CNS infection, and head trauma (see Table 2). (33) Among children hospitalized with gastroenteritis or febrile illness, plasma ADH levels were found to be inappropriately increased in children with hyponatremia at admission. (9)(34) Furthermore, administration of hypotonic IV fluids has been shown to increase risk for the development of hyponatremia after hospital admission. (10) A recent meta-analysis of available randomized clinical trials in children demonstrated that the relative risk for hyponatremia among children receiving hypotonic IV fluids was 2.37 (range, 1.72–3.26), with relative risk for moderate hyponatremia (<130 mEq/L [<130 mmol/L]) of 6.1 (range, 2.2–17.3). (35) These findings were similar to those previously reported in a meta-analysis, which included cohort studies and available randomized trials of hypotonic versus isotonic fluid. (36) Over the past 2 decades, experts have urged clinicians to change from the classic approach to fluid and electrolyte management, as outlined by Holliday et al, to a preference of isotonic fluids for maintenance therapy. (32)(33)(37) Exceptions to this include children with increased ongoing water loss, such as renal concentrating defects and extrarenal losses of fluid.

When Moritz and Ayus published their argument that using isotonic IV fluids, such as normal saline or lactated Ringer solution, would prevent hospital-acquired hyponatremia, (33) a debate was initiated between their proposal and the standard parenteral fluid therapy originally outlined by Holliday et al, adopted universally by practicing pediatricians and taught to pediatric house staff for decades. (38)(39) While acknowledging that many hospitalized children are at risk for alternations in renal water excretion due to nonosmotic stimuli for ADH secretion, those in favor of the method of Holliday et al postulated that the use of isotonic fluid would result in hypernatremia and/or fluid overload. (40) Most importantly, IV fluid should be prescribed with the same care as other medical treatments and medications, and the patient must be carefully monitored.

In summary, hyponatremia is relatively common, particularly in hospitalized children who are at risk for SIADH.

SUMMARY

1. On the basis of strong research evidence (level A), administration of isotonic fluid is recommended as the first choice for intravenous (IV) fluid in hospitalized children. (10)(15)(16)(35)(36)(37)
2. On the basis of primarily consensus, due to lack of relevant clinical studies (level D), careful monitoring of serum electrolyte levels is required after initiation of IV fluids to avoid hyponatremia. (4)(41) Evaluation of children with hyponatremia is aimed at determining the underlying cause so that treatment can be appropriately outlined.
3. On the basis of strong research evidence (level B), symptomatic hyponatremia deserves immediate treatment with hypertonic saline, but thereafter, hyponatremia should be corrected slowly to avoid further central nervous system sequelae. (2)(4)(7)(8)(42)
4. On the basis of some research evidence, as well as consensus (level C), syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common underlying cause of hyponatremia in children, and most cases are acute and transient conditions. (9)(11)(14)(33)(34)
5. In cases of chronic hyponatremia due to SIADH, treatment options, in addition to fluid restriction, include furosemide, urea, and tolvaptan; treatment recommendations are largely based on some research evidence, as well as consensus (level C). (8)(17)(22)(23)(24)(25)(26)(27)(28)
6. More information will be needed to guide specific recommendations regarding the ideal choice of therapy for children with chronic hyponatremia.

References for this article are at http://pedsinreview.aappublications.org/content/39/1/27.

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1. A 5-year-old boy is brought to the emergency department with a 5-day history of vomiting and diarrhea. His parents report a 1.6-kg weight loss. He has been drinking only water. His physical examination findings show signs of moderate volume depletion, with a heart rate of 110 beats/minute. He has not produced any urine for at least a few hours. His laboratory values are sodium level of 130 mEq/L (130 mmol/L), potassium level of 5 mEq/L (5 mmol/L), bicarbonate level of 15 mmol/L, chloride level of 110 mEq/L (110 mmol/L), creatinine level of 1.0 mg/dL (88.4 μmol/L), blood urea nitrogen (BUN) level of 20 mg/dL (7.14 mmol/L), blood glucose level of 100 mg/dL (5.55 mmol/L), serum osmolality of 271 mmol/kg, and urine sodium level of $<$5 mmol/L. Which of the following mechanisms is likely to be occurring in this child?
   - A. Decreased baroreceptor response to volume depletion.
   - B. Decreased thirst due to hypo-osmolality.
   - C. Increased antidiuretic hormone (ADH) secretion response to hypovolemia.
   - D. Increased cell volume due to water retention.
   - E. Increased sodium excretion due to hypovolemia.
2. A 4-year-old girl is brought to the emergency department with cough and fever measured at home at 104°F (40°C). At physical examination, she has rales in the right lower lung field, and a chest radiograph shows a right lower lobe infiltrate. Her parents refuse blood tests and intravenous (IV) line placement and request only oral treatment. What is the likelihood that this child has a serum sodium level less than 135 mEq/L (135 mmol/L) at this time?
   - A. 1% to 5%.
   - B. 5% to 10%.
   - C. 10% to 15%.
   - D. 20% to 45%.
   - E. 60% to 75%.
3. The patient described in question 2 progresses to worsening tachypnea and hypoxia. Her oxygen saturation level is 90%, with 2 L delivered via nasal cannula. Her parents agree to allow IV placement and inpatient admission. Her serum electrolyte levels are sodium level of 134 mEq/L (134 mmol/L), potassium level of 3.5 mEq/L (3.5 mmol/L), bicarbonate level of 28 mEq/L (28 mmol/L), and chloride level of 110 mmol/L. What is the best IV fluid choice for maintenance fluid delivery for this patient?
   - A. 5% dextrose with 0.35 normal saline.
   - B. 0.22 ("quarter-normal") saline with 20 mEq/L KCl.
   - C. 5% dextrose with 0.22 ("quarter-normal") saline and 5 mEq/L KCl.
   - D. 5% dextrose with 0.45 ("half-normal") saline and 10 mEq/L KCl.
   - E. 5% dextrose with 0.9 ("normal") saline and 10 mEq/L KCl.
4. An 8-year-old boy is referred to the emergency department with a history of headache for the past 24 hours and nausea and vomiting for the past 7 days. Serum sodium level measured at an urgent care center was 120 mEq/L (120 mmol/L). His past medical history is unremarkable. Physical examination shows heart rate of 100 beats/minute, blood pressure of 80/35 mm Hg, and dry mucous membranes. His laboratory values are sodium level of 120 mEq/L (120 mmol/L), potassium level of 3.2 mEq/L (3.2 mmol/L), bicarbonate level of 25 mEq/L (25 mmol/L), chloride level of 89 mEq/L (89 mmol/L), and osmolality level of 275 mmol/L. Urine sodium level is $<$10 mmol/L, and specific gravity is higher than 1.030. Which of the following diagnoses is most likely to explain his electrolyte abnormalities?

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A. Cerebral salt wasting.
B. Congestive heart failure.
C. Gastroenteritis.
D. Renal failure.
E. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

5. A previously healthy 9-year-old girl is seen for evaluation of headache and mild nausea that has developed gradually over the past 2 or 3 weeks. She has not had any vomiting or diarrhea, although her appetite seems to have decreased. She is not taking any medications. Her heart rate is 75 beats per minute, and her blood pressure is 90/50 mm Hg. Her physical examination findings show no abnormalities, except for tenderness over her right pelvic brim. She has no edema. Her laboratory values include sodium level of 118 mEq/L (118 mmol/L), potassium level of 3.8 mEq/L (3.8 mmol/L), bicarbonate level of 22 mEq/L (22 mmol/L), chloride level of 90 mEq/L (90 mmol/L), BUN level of 4 mg/dL (1.43 mmol/L), creatinine level of 0.5 mg/dL (44.20 μmol/L), and serum osmolality of 250 mmol/kg. Urine sodium level is 45 mEq/L (45 mmol/L), and urine osmolality is 400 mOsm/kg (400 mmol/kg). Which of the following diagnoses is most likely to explain her hypo-osmolar state?

   A. Congestive heart failure.
   B. Gastroenteritis.
   C. Hepatic failure.
   D. Psychogenic polydipsia.
   E. SIADH.

Index of Suspicion

1

Unilateral Leg Pain and Difficulty Walking

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Shah, Diaz-Medina, and Chen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-year-old boy presents with unilateral leg pain and difficulty walking for 6 days. During that time, the patient developed a fever and an upper respiratory tract infection. Physical examination shows no edema, erythema, or warmth in the lower extremities. There is tenderness to palpation of the right lower extremity (RLE). There is also pain on passive and active range of motion (ROM) testing as well as decreased muscle strength in the RLE. The right patellar and Achilles reflexes are absent. The left lower extremity, however, shows unaffected ROM and muscle strength testing, with the patellar and Achilles reflexes diminished to 1/4+. When prompted to walk, the patient limps and is unable to bear weight on his RLE. Findings on radiographs of the hips and RLE and magnetic resonance images (MRIs) of the hips are all normal. Lumbar puncture shows a normal white blood cell count with an increased protein level, as well as elevated immunoglobulin G (IgG) levels. The MRI of the thoracic and lumbar spine shows abnormal enhancement of ventral and dorsal nerve roots extending off the conus and filum terminale into the cauda equina (Fig 1). In addition, there is particularly asymmetrical enhancement of the right dorsal nerve roots versus the left in the lumbar spine (Fig 2). Nerve conduction studies show axonal polyneuropathy in the bilateral lower extremity nerves tested and borderline decreased conduction velocity (abnormal findings

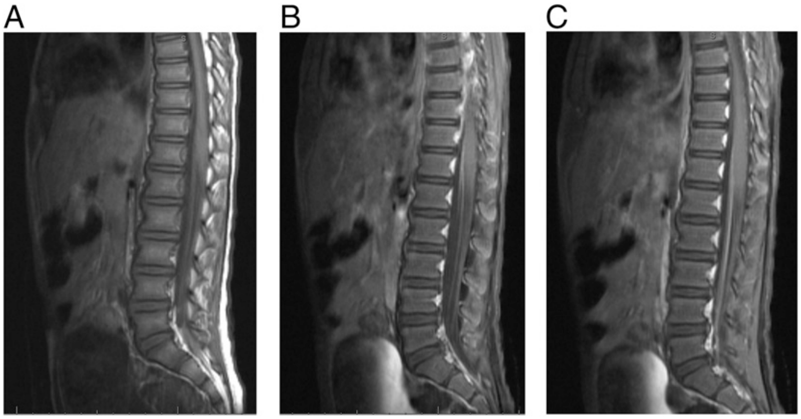

Figure 1. Sagittal T1 magnetic resonance images (A) without contrast and (B and C) with contrast. Abnormal enhancement of the ventral and dorsal nerve roots extending off the conus and filum terminale into the cauda equina can be seen.

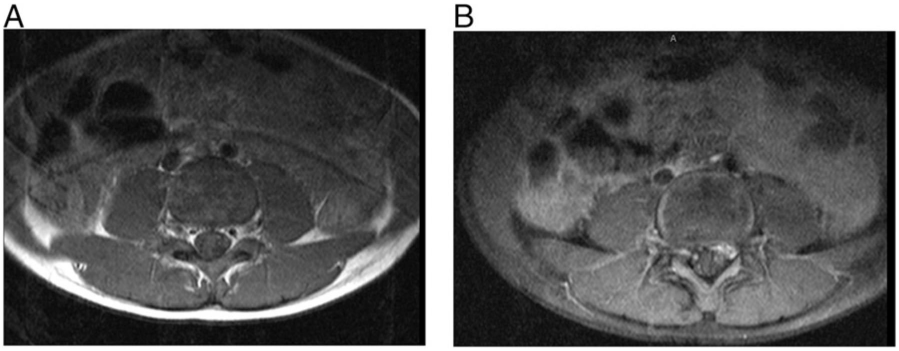

Figure 2. Axial T1 magnetic resonance images (MRIs) (A) without contrast and (B) with contrast. Particularly, asymmetrical enhancement of the right dorsal nerve roots versus the left can be seen in the MRI with contrast.

TABLE 1. Motor Peripheral Nerve Conduction Study

NERVE	mA-ms	DML, ms	DML, mm	DMA, mV	NCV, m/s	NORMAL DML, ms	NORMAL DMA, mV	NORMAL NCV, m/s
Left peroneal	100/0.2	4.1	60	1.7	45.8	6.5	2	44
Right peroneal	100/0.2	5.1	60	0.4	42.3	6.5	2	44

DMA=distal motor amplitude, DML=distal motor latency, NCV=nerve conduction velocity.

TABLE 2. Sensory Peripheral Nerve Conduction Study

NERVE	mA-ms	DSL, ms	DSL, mm	DSA, μV	NCV, m/s	NORMAL DSL, ms	NORMAL DSA, μV	NORMAL NCV, m/s
Left sural	94/0.2	1.9	60	24.3	34	4.4	6	40
Right sural	16.4/0.2	2.0	60	12.8	34	4.4	6	40

DSA=distal sensory amplitude, DSL=distal sensory latency, NCV=nerve conduction velocity.

TABLE 3. F-Response Study (Indicates Conduction Block and/or Axonal Loss)

NERVE	mA-ms	M-LATENCY, ms	F-WAVE LATENCY, ms	NORMAL F-WAVE LATENCY, ms
Right peroneal	100/0.2	5.1	Absent response	≤56

summarized in Tables 1-3). Electromyography testing finds positive waves and fibrillations and decreased recruitment. All of this testing together reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/1/36.

DISCUSSION

The case illustrates a patient newly diagnosed as having Guillain-Barré syndrome (GBS) who atypically presented with unilateral leg pain. The ascending paralysis of GBS is classically bilateral and can be rapidly progressive, so diagnosis needs to be made promptly. Symptoms of GBS may include distal lower extremity weakness, cranial nerve involvement leading to facial muscle weakness, ataxia, muscular or radicular pain in the spinal region, symptoms of a preceding infection, and reduced tendon reflexes in the involved extremities. (1)(2) Progression of weakness can occur within a few hours to days, which is why swift diagnosis can prove to be crucial.

The diagnosis can be challenging, notably in children, atypical presentations, and patients reporting pain initially. Our patient fell into each of these categories. The patient reported limited ROM secondary to pain. It has been seen that pain can present in more than 44% of children with GBS. (2) Given this symptom, the differential diagnosis included trauma, such as a strain; inflammation, such as transient synovitis or juvenile rheumatoid arthritis; congenital conditions, such as hip dysplasia; infection, such as discitis, and more. The differentiation and physical examination finding that the patient's RLE difficulty was primarily weakness and not pain, combined with loss of deep tendon reflexes, is what led to performing a more complete neurologic examination.

Conditions that can be considered include poliomyelitis, acute flaccid myelitis, syringomyelia, acute disseminated encephalomyelitis, and more. Poliomyelitis is an infectious disease of the anterior horn motor neurons of the spinal cord and brain stem. Flaccid, asymmetrical weakness and muscle atrophy are common, thus the overlap in clinical presentation with this patient is clear. The polio-like acute flaccid myelitis can involve a febrile or respiratory illness before neurologic symptoms, similar to GBS. The Centers for Disease Control and Prevention (CDC) confirmed 277 cases of this pathologic condition from August 2014 to December 2016 alone. Manifestations include limb weakness or paralysis and variable cranial nerve involvement. Evidence of spinal gray matter lesions can be seen on MRI with this condition. (3) Syringomyelia involves the formation of a fluid-filled cavity or cyst in the spinal cord. Presentation can include chronic pain or loss of pain and temperature sensation, weakness, paralysis, or disruption to parasympathetic or sympathetic function. Acute disseminated encephalomyelitis is an immune-mediated demyelinating disease that is also often postinfectious. Manifestations include the systemic signs and symptoms of encephalopathy and can progress to pyramidal signs, hemiparesis, cranial neuropathy, and more. All of these pathologic conditions and others were kept in mind during the neurologic evaluation, but we would find that GBS would be the prevailing diagnosis in the end.

Although GBS is a clinical diagnosis, further testing can be valuable for validation. On examination of the patient's cerebrospinal fluid, the classic GBS finding of cytoalbuminologic dissociation was present, as well as increased IgG levels. It has been shown that IgG levels in cerebrospinal fluid may be elevated in patients with GBS; one of the disease variants, acute motor axonal neuropathy, involves antiganglioside antibodies, which are IgG in class. (4)(5)

The patient's postcontrast MRI showed the typical GBS findings of surface thickening and contrast enhancement on the conus medullaris and nerve roots of the cauda equina. (6) More commonly in GBS, this enhancement is of the ventral nerve roots, but as with our patient it can also be seen dorsally. Nerve conduction studies are essential for classification between variants of GBS, such as acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy. Findings from these studies can show overlap of the variants, as with our patient.

The general treatment protocol for GBS includes hospital admission and intravenous immunoglobulin, 400 mg/kg per day for 5 days, or plasma exchange. If there is a treatment-related fluctuation, which is deterioration after initial stabilization or improvement, repeated treatment with the same course should be used. During acute presentation, monitoring of respiration, swallowing difficulties, progression of weakness, and autonomic dysfunction is paramount. Disease severity and duration vary in patients and can range from minor weakness with spontaneous recovery to quadriplegia and ventilator dependency without signs of improvement for months or longer. Approximately 20% to 30% of those with GBS progress to respiratory failure and need to be placed in an ICU for ventilation. (1)(2) Autonomic dysfunction can include systemic hypertension, widely fluctuating blood pressures, arrhythmias that can require pacemaker placement, ileus, or bladder paralysis. Mortality occurs from these complications, and in Europe and North America it ranges from 3% to 7% of patients with GBS. Emergencies arise most often when diagnosis is delayed, particularly in young children. Patients with GBS often have enduring ailments, such as fatigue and pain, due to lasting axonal loss, and these can have a marked effect on quality of life. Unfortunately, approximately 20% of patients with GBS cannot walk unaided 6 months after disease onset. (1)

In summary, GBS has the potential for major morbidity and mortality. With this patient, it was important to perform a careful and thorough physical examination to establish a broad differential diagnosis that included GBS. Because of the diagnostic difficulty due to the patient's atypical presentation, it was important to evaluate the patient with a lumbar puncture, MRI, and nerve conduction studies.

Lessons for the Clinician

- Symptoms of Guillain-Barré syndrome (GBS) may include distal lower extremity weakness, cranial nerve involvement leading to facial muscle weakness, ataxia, muscular or radicular pain in the spinal region, symptoms of a preceding infection, and reduced tendon reflexes in the involved extremities.
- Diagnosis is clinical and can be challenging, notably in children, atypical presentations such as those with unilateral symptoms, and patients reporting pain initially. Differential diagnoses include poliomyelitis, acute flaccid myelitis, syringomyelia, acute disseminated encephalomyelitis, and more.
- Lumbar puncture, magnetic resonance imaging, and nerve conduction studies can help bolster the diagnosis.
- The general treatment protocol for GBS includes hospital admission and intravenous immunoglobulin, 400 mg/kg per day for 5 days, or plasma exchange.
- Because the ascending paralysis of GBS can be rapidly progressive and cause respiratory failure and/or autonomic dysfunction, diagnosis and treatment need to be performed promptly.

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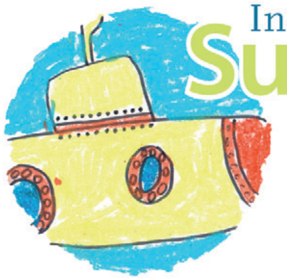

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2

Refusal to Walk in a 2-year-old Girl

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AUTHOR DISCLOSURE Drs Bashir and Aarons have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year-old girl presents with refusal to walk. Her symptoms started 3 weeks ago at child care with fever (104°F [40°C]) and difficulty bearing weight on both lower extremities. A bilateral lower extremity radiograph taken at a local emergency department at that time was unremarkable, but she was found to have acute otitis media and was treated with a course of amoxicillin. After a week the child's limp worsened, causing her to seek treatment at a community clinic, where she was prescribed ibuprofen and heating pads. The progression of symptoms brings her to our hospital. There is no history of trauma or respiratory symptoms. Three months ago she had an episode of bloody diarrhea positive for *Escherichia coli* and *Shigella*. Her immunization record is up-to-date.

On physical examination, she appears comfortable and alert. Her temperature is 98.4°F (36.9°C), heart rate is 100 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 84/60 mm Hg. Examination of her lower extremities is limited due to poor cooperation. It is difficult to determine whether the patient has leg tenderness because lower extremity motion elicits pain. There seems to be full range of motion bilaterally of the hips and knees. Deep tendon reflexes cannot be elicited in the lower extremities at both knees and ankles. There seems to be a slight increase in muscle tone of the lower extremities, but this can be due to an examination error. There is limited dorsiflexion of the right foot. There is no swelling or erythema at any of the joints in the lower extremities. The remainder of the examination findings are normal.

Her complete blood cell count, comprehensive metabolic panel, creatine kinase level, antinuclear antibodies, and C-reactive protein (CRP) level are all within their respective normal ranges. The erythrocyte sedimentation rate (ESR) is slightly elevated at 25 mm/hour. Lower extremity radiographic and bone scan findings are negative. Additional evaluation leads to the diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/1/38.

DISCUSSION

Magnetic resonance imaging (MRI) of the spine demonstrated inflammatory demyelinating polyneuropathy, and a cerebrospinal fluid (CSF) analysis showed normal white and red blood cell counts and a high protein concentration of 0.1 g/dL (1.0 g/L), thus establishing the diagnosis of Guillain-Barré syndrome (GBS). The patient was treated with intravenous immunoglobulin (IVIg) and was then transferred to a rehabilitation center for continued care.

The Condition

Guillain-Barré syndrome is a postinfectious polyneuropathy involving mainly motor nerves, but it can also affect sensory and autonomic nerves. It is the most common cause of acute flaccid paralysis in the pediatric population. A preceding diarrheal infection with *Campylobacter jejuni* is most commonly associated with GBS. However, infections with Epstein-Barr virus, cytomegalovirus, and mycoplasma pneumoniae have also been associated with the development of GBS.

The classic presentation of GBS is an acute ascending flaccid paralysis, but many clinical variants exist. Weakness is usually symmetrical and begins in the lower extremities progressing upward toward the trunk. There is often associated paresthesia and pain contributing to inability to walk. Classically, deep tendon reflexes are lost, although they may be preserved until late in the disease. Involvement of the diaphragm can lead to respiratory compromise, and these patients may need mechanical ventilation. Dysphagia and facial weakness can be subtle signs of impending respiratory failure. Some patients experience autonomic instability, leading to hypotension or hypertension, cardiac dysrhythmias, bladder dysfunction or abnormal sweating. Thus, these patients require close cardiorespiratory monitoring. The severity of illness greatly varies among individuals, with some progressing over hours and others over weeks.

Differential Diagnosis

The differential diagnosis of a limping child is broad. One of the most common causes of limping in young children is toxic synovitis. It is usually preceded by an upper respiratory tract infection and responds well to nonsteroidal anti-inflammatory drugs and heating pads. Another diagnosis we considered was juvenile idiopathic arthritis, but lack of a rash, joint swelling, erythema, or warmth makes it less likely.

Infectious etiologies such as septic arthritis, postinfectious myositis, and osteomyelitis were also considered. These would present with fever, and laboratory studies would show elevated CRP levels and leukocytosis on complete blood cell count. The bone scan results would be positive, showing focally increased uptake and focal hyperemia. Diskitis is another condition that has an acute onset in children and that can present with refusal to walk and a normal white blood cell count; however, the CRP level and ESR would be significantly elevated.

Ultimately, concern for spinal cord lesions and demyelinating diseases prompted a spinal MRI. Her clinical history, physical examination, MRI, and then CSF findings support the diagnosis of GBS.

The Diagnosis

The diagnosis is established by a combination of clinical presentation (preceding gastrointestinal or respiratory tract infection, progressive weakness, pain, paresthesia, and areflexia) combined with CSF analysis, MRI of the spinal cord, and, occasionally, electrodiagnostic studies or antibody studies. Analysis of CSF usually demonstrates elevated CSF protein levels (>0.045 g/dL [0.45 g/L]), with a normal CSF leukocyte count. This is known as albuminocytologic dissociation. The CSF protein level may not be elevated early in the course of the disease.

Management

Treatment of GBS consists of supportive care and administration of IVIg or plasma exchange. The use of IVIg is preferred in the pediatric population because plasma exchange is an invasive and time-consuming procedure. Regardless, both treatments yield excellent recovery in the pediatric population compared with adults. The mortality rate is 3% to 4%, with a recurrence rate of 2% to 5%.

Lessons for the Clinician

- Guillain-Barré syndrome should be considered in the differential diagnosis of a child with a limp.
- Classically, deep tendon reflexes are lost, although they may be preserved until late in the disease.
- Dysphagia and facial weakness can be subtle signs of impending respiratory failure.
- Making an accurate diagnosis in a timely manner can help avoid unwanted consequences of Guillain-Barré syndrome, such as diaphragm paralysis requiring mechanical ventilation and cardiac arrhythmias.

Suggested Readings

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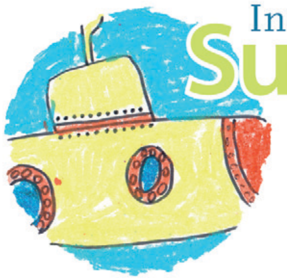

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Ophthalmoplegia and Unsteady Gait in an 11-year-old Boy

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AUTHOR DISCLOSURE Drs Bassal and Lupo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 11-year-old boy is admitted to the hospital for 2 days of new-onset blurry vision, diplopia, and unsteady gait. He denies recent trauma, dizziness, weakness, headaches, nausea, vomiting, diarrhea, fever, and travel. The patient denies recent ingestion of alcohol, illicit drugs, medications, or toxins. Further questioning reveals a 1-day history of coughing, sneezing, and watery eye discharge occurring 1 week earlier that seemingly improved after antihistamine use.

On admission, his vital signs are as follows: temperature, 98.5°F (36.9°C); pulse, 83 beats/min; respiratory rate, 18 breaths/min; blood pressure, 129/86 mm Hg; and oxygen saturation, 100% in room air. Physical examination reveals a well-nourished boy with appropriate affect and mentation. Ophthalmologic examination is significant for left esotropia and mild bilateral hypertropia. Extraocular movements are painless, with incomplete abduction of both eyes, worse on the left. Consensual pupillary response is absent, and the pupils are dilated to 7 mm at baseline, with a sluggish direct response to light. There is no optic nerve edema. Neurologic examination is otherwise significant for dysmetria, which improves somewhat with covering 1 eye, and a tentative gait with unsteadiness concerning for gait ataxia. Reflexes are difficult to elicit but present, and there is no muscle weakness.

Urine toxicology screen is negative. Head computed tomography and brain magnetic resonance imaging findings are normal. Lumbar puncture reveals an opening pressure of 17 cm H_2O. Cerebrospinal fluid (CSF) analysis reveals no white blood cells, a protein level of 0.028 g/dL (0.28 g/L), and a glucose level of 65 mg/dL (3.6 mmol/L). Results of CSF and serum viral studies are negative.

The patient's vital signs and condition remain stable, but reflexes are absent on examination the following day. Treatment is initiated based on clinical findings, and a serum antibody test confirms the clinical suspicion.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/1/39.

DISCUSSION

Differential Diagnosis

The initial differential diagnosis for this patient with cranial nerve VI and cranial nerve III dysfunction and gait problems (likely ataxia) with preserved strength and cognition included intracranial tumor, central nervous system infection, demyelinating disease, Guillain-Barré syndrome (GBS), intoxication, and acute cerebellar ataxia.

Because neuroimaging results were normal, we were able to rule out tumor and some forms of demyelinating disease, such as acute demyelinating encephalomyelitis and multiple sclerosis. Urine drug screen acetaminophen and salicylate levels were negative, making toxic ingestion unlikely. Our patient did not have a fever or signs of infection, and human immunodeficiency virus (HIV) serology was negative. Results of serum and CSF herpes simplex virus, varicella-zoster virus, and enterovirus studies were also negative.

When his cranial nerve abnormalities persisted and he began to have more definitive ataxia on examination and absent tendon reflexes, the diagnosis of GBS, especially the Miller Fisher syndrome (MFS) variant, became much more likely. Although albuminocytologic dissociation is expected on CSF studies, this abnormality is often not present early in the course of the disease.

With GBS in mind, we sent a serum ganglioside antibody panel, which returned significant for elevation of antiganglioside anti-GQ1b immunoglobulin G antibody, confirming our diagnosis of the MFS variant of GBS.

The Condition

The MFS is rare, with an incidence of 1 in 1 million and accounting for 5% of patients with GBS. (1) Clinically, it consists of the classic triad of areflexia, ataxia, and ophthalmoplegia. (2) Our patient displayed this triad during his hospital admission, although the areflexia developed later in the course. His oculomotor paresis came in the form of cranial nerve VI palsy demonstrated by left esotropia with incomplete eye abduction, in addition to cranial nerve III palsy evidenced by hypertropia and the pupillary findings, which are likely secondary to the nerve's efferent limb for consensual light reflex. The ophthalmoplegia characteristic of MFS is particularly associated with an elevation of antiganglioside anti-GQ1b immunoglobulin G antibody, which is elevated in more than 90% of patients. (3)

Because MFS is a rare variant of GBS, it results from peripheral nerve demyelination after an initial insult is thought to spur an autoimmune response. (1) The most common inciting cause is an infectious process, with *Campylobacter jejuni* being the most commonly implicated. This is thought to occur through molecular mimicry, as studies have demonstrated that lipopolysaccharide epitopes from *C jejuni* may mimic human gangliosides, leading to cross reactivity in affected patients. (4) GQ1b is one such antiganglioside antibody and is notably concentrated in the cranial nerves, particularly III and VI, as demonstrated by cranial nerve enhancement on neuroimaging studies. (5)

There are numerous other infectious etiologies for MFS reported, including HIV, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, *Escherichia coli*, influenza A, and mumps. Additional causes include various cancers, autoimmune conditions, and tumor necrosis factor inhibitor medication. (6) Our patient's case is unique in that the most probable inciting cause was an episode that resembled allergic rhinitis based on the symptom description and improvement after diphenhydramine and cetirizine therapy. To the author's knowledge, this is the only such case of MFS in the literature caused by allergic rhinitis.

Management and Outcomes

The standard treatment for MFS is intravenous immunoglobulin (IVIg) or plasmapheresis, as it is in GBS. A retrospective study by Mori and colleagues demonstrated that IVIg therapy slightly sped up the recovery of ophthalmoplegia and ataxia in patients with MFS. (7) However, IVIg therapy and plasmapheresis are not warranted for all affected individuals. In fact, mildly affected patients may be closely observed because most patients have good outcomes, with recovery at 10 weeks on average. (8) Although MFS rarely includes dysautonomia or progresses to respiratory failure, as is more commonly seen with standard GBS, approximately one-third of patients have residual symptoms, and there are rare cases of recurrence, with a notable case report describing 2 children with recurrent MFS. (9)

Our patient was treated with IVIg 400 mg/kg per dose for 5 doses. By the time of hospital discharge, he remained areflexic, with improvement of his gait and double vision. On neurology clinic follow-up 2 weeks after discharge, he was noted to have a normal pupillary response to light but still had lateral gaze palsy. Intermittent eye patching provides comfort, and he is back in school, although he needs extra time to get to and from classes. As of the time of this report, he continues to follow up with outpatient neurology and neuro-ophthalmology.

Lessons for the Clinician

- Miller Fisher syndrome (MFS) is a rare variant of Guillain-Barré syndrome that presents with the triad of areflexia, ataxia, and ophthalmoplegia.
- Although *Campylobacter jejuni* is often implicated, there are various other inciting factors leading to the autoimmune response causing the disease.

- When suspected, serum antiganglioside studies should be analyzed because elevation of antiganglioside anti-GQ1b immunoglobulin G antibody is highly specific for MFS.
- Intravenous immunoglobulin therapy has been shown to slightly accelerate recovery in MFS and should be used in severe cases.

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Hypoglycemia after Nissen Fundoplication in a 7-month-old Girl

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AUTHOR DISCLOSURE Drs Krishnamurthy, Chandra, and Henwood-Finley have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 7-month-old girl underwent a Nissen fundoplication for severe gastroesophageal reflux. On postoperative day 5, she was found to be sweating profusely, and her hands and feet felt moist. Her blood glucose level at the time was 32 mg/dL (1.8 mmol/L). Serial measurements of blood glucose levels before and after meals over a 48-hour period demonstrated preprandial hypoglycemia (blood glucose level, 32 mg/dL [1.8 mmol/L]) and postprandial hyperglycemia (blood glucose level, 233 mg/dL [12.9 mmol/L]) (Fig 1). When hypoglycemia recurred, a critical sample was collected to rule out possible etiologies of hypoglycemia, including congenital hyperinsulinism, growth hormone deficiency, cortisol deficiency, fatty acid oxidation defects, organic acid disorders, and iatrogenic causes.

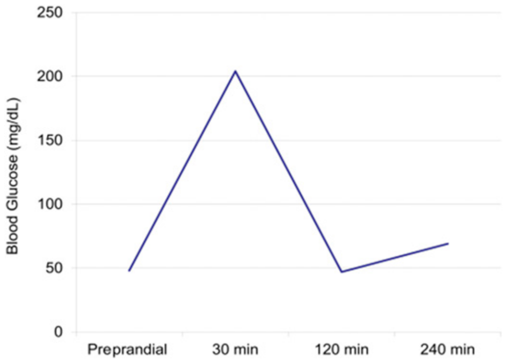

Figure 1. Preprandial and postprandial blood glucose levels.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/1/40.

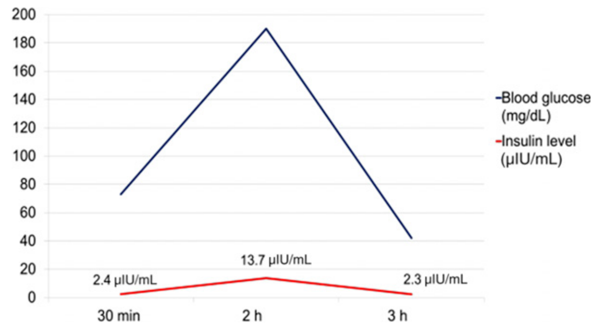

Figure 2. Diagnostic evaluation of dumping syndrome showing postprandial blood glucose and insulin levels.

DISCUSSION

Our patient's pattern of postprandial hyperglycemia followed by hypoglycemia suggested dumping syndrome. The diagnosis was confirmed by laboratory testing, which showed a rise in insulin levels from 2.4 μIU/mL (16.7 pmol/L) at baseline to 13.7 μIU/mL (95.2 pmol/L) 30 minutes after a feeding followed by a decline to 2.3 μIU/mL (16.0 pmol/L) 90 minutes after a feeding while her postprandial glucose readings increased to 190 mg/dL (10.5 mmol/L) and then fell to 42 mg/dL (2.3 mmol/L) by the conclusion of the test (Fig 2). Acarbose is a medication that inhibits α-glucosidase in the intestinal brush border and is used in the treatment of type 2 diabetes in adults. It was started at an initial dose of 12.5 mg 3 times a day. Preprandial blood glucose levels improved to greater than 70 mg/dL (>3.9 mmol/L) 3 hours and sometimes 6 hours after feedings, but she continued to have readings less than 70 mg/dL (<3.9 mmol/L) after feedings not associated with a dose of acarbose. The dose of acarbose was then increased to 25 mg 3 times a day. She maintained all blood glucose readings greater than 70 mg/dL (>3.9 mmol/L) and was discharged with this dose of acarbose (Fig 3).

Awareness of dumping syndrome as a possible complication after Nissen fundoplication helps facilitate rapid diagnosis and treatment.

The Condition

Dumping syndrome is a common complication of Nissen fundoplication, especially in pediatric patients. Dumping syndrome can be classified into 2 types: early (osmotic) and late (hypoglycemic) (Fig 4). Both types are associated with a large volume of gastric content entering the duodenum or jejunum, resulting in symptoms of dumping, including sweating, tachycardia, abdominal pain, nausea, and diarrhea. Moreover, the symptoms of dumping syndrome can be divided into vasomotor or gastrointestinal. Vasomotor symptoms include tachycardia, sweating, flushing, palpitations, and dizziness, and gastrointestinal symptoms include nausea, cramping, abdominal pain, and diarrhea.

Early or osmotic dumping occurs up to 45 minutes after a meal and results from passage of a large volume of osmotic material into the small bowel. This causes an influx of fluid from the intravascular space. There is a subsequent reduction in circulating volume, resulting in release of vasoactive peptides, including vasoactive intestinal peptide, causing the symptoms described previously herein.

Late or hypoglycemic dumping occurs 2 to 4 hours after a meal and is due to rapid delivery of glucose into the duodenum. Consequently, a rapid increase in serum glucose levels

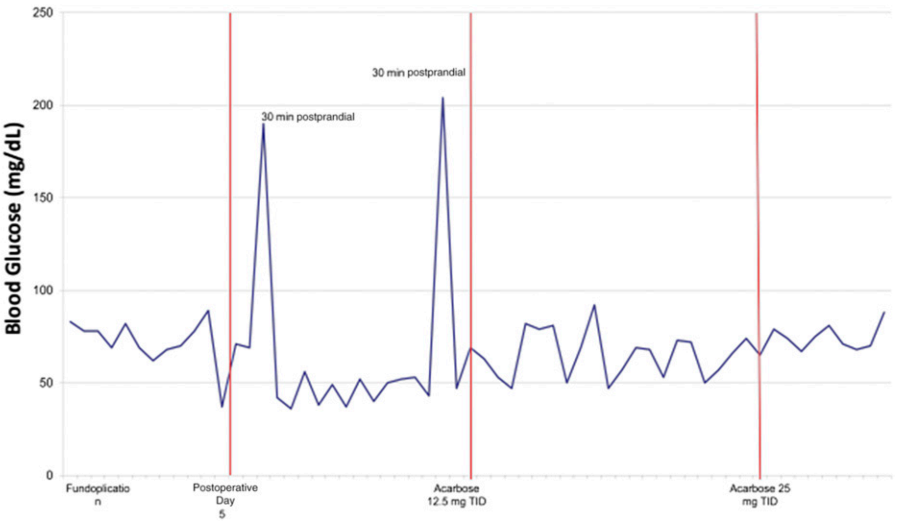

Figure 3. Blood glucose levels before and after intervention with acarbose. All blood glucose values are obtained immediately preprandial unless labeled otherwise.

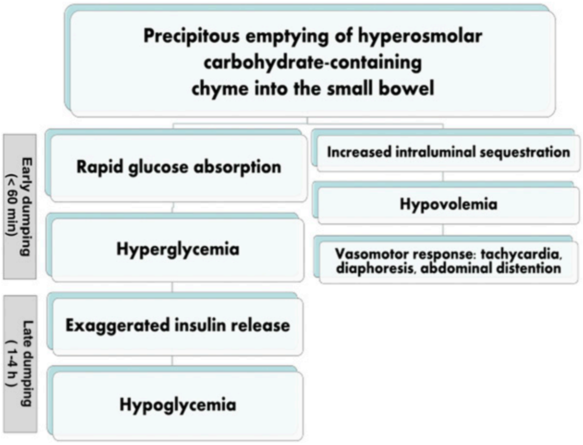
Precipitous emptying of hyperosmolar carbohydrate-containing chyme into the small bowel
Early dumping (< 60 min)
Rapid glucose absorption
Increased intraluminal sequestration
Hypovolemia
Hyperglycemia
Vasomotor response: tachycardia, diaphoresis, abdominal distention
Late dumping (1-4 h)
Exaggerated insulin release
Hypoglycemia

Figure 4. Pathophysiology of dumping syndrome.

results in excessive insulin secretion, leading to hypoglycemia. Symptoms of late dumping syndrome are much more subtle and nonspecific compared with those of early dumping syndrome. Confirmation of late dumping syndrome requires demonstration of hypoglycemia after an oral glucose tolerance test.

Clinical Presentation

Dumping syndrome is a common complication after gastric surgery in adults but is not as well described in infancy and childhood. There are relatively few case reports and studies describing dumping syndrome in children. This may be because children lack classic gastrointestinal symptoms of early dumping and have severe postprandial hyperglycemia as a first sign, which often goes unrecognized.

Diagnosis

The first step to making a diagnosis of dumping syndrome is to obtain a detailed history. If the patient has had previous gastrointestinal surgery, such as a Nissen fundoplication, this may be a clue to the clinician that the patient may have dumping syndrome. Moreover, symptoms of hypoglycemia a few hours after a meal, such as sweating, tachycardia, and gastrointestinal symptoms, including bloating, abdominal cramping or pain, and diarrhea, should raise clinical suspicion for dumping syndrome.

Once dumping syndrome is on the list of differential diagnoses, it is important to obtain blood glucose and insulin levels every 30 minutes for 2 to 3 hours after feeding. This will help establish the pattern of postprandial hyperglycemia followed by hypoglycemia. An oral glucose tolerance test is helpful to provoke symptoms of early dumping syndrome and to evaluate for late reactive hypoglycemia. A decrease of more than 108 mg/dL (>6 mmol/L) between peak and nadir blood glucose measurements has been proposed as diagnostic criteria for dumping syndrome. Continuous glucose monitoring has also been used to clearly detect large glycemic fluctuations around times of feeding. This modality has been helpful in ensuring that treatment ameliorates rapid changes in glucose.

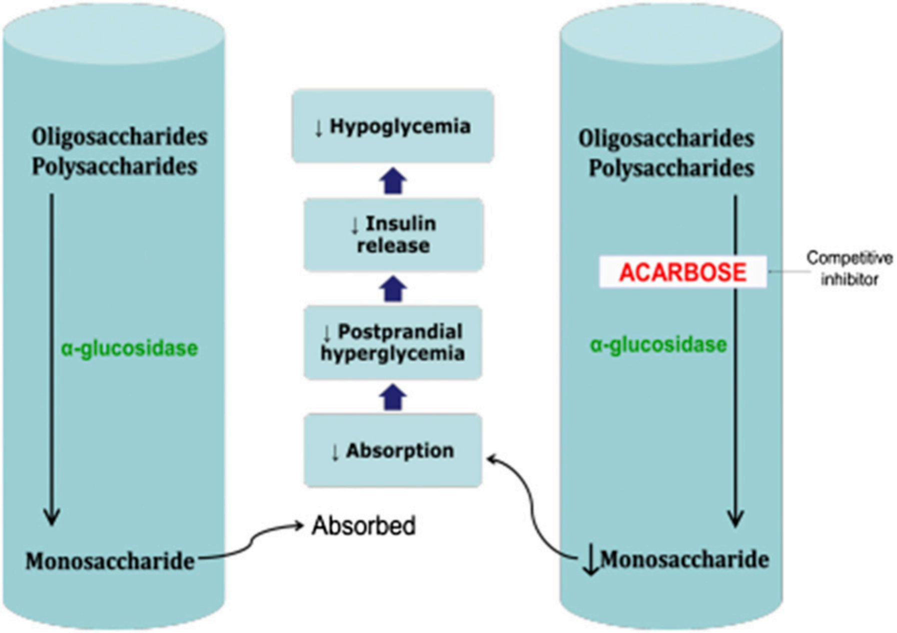

Figure 5. Mechanism of action of acarbose.

Management

Dietary modifications are the first step to inhibiting rapid gastric emptying. These changes include adding complex carbohydrates such as raw uncooked cornstarch or switching to infant formulas with higher complex carbohydrate content. Small feeding volumes and restricting fluid intake also help minimize the intragastric pressure that promotes rapid emptying of stomach contents into the duodenum. There are some reports of continuous feeding regimens to avoid large fluxes in blood glucose levels, but this may decrease mobility and delay development of oral feeding skills in children. The use of α-glucosidase inhibitors such as acarbose has been studied in children with dumping syndrome. Acarbose interferes with the conversion of polysaccharides and reduces rapid carbohydrate absorption (Fig 5). Doses as low as 12.5 mg to start have been useful in helping achieve desired ranges of blood glucose without the adverse effects of flatulence, abdominal distention, and diarrhea. If children are administered acarbose for dumping syndrome, liver function tests should be closely monitored.

Lessons for the Clinician

- Dumping syndrome can result from Nissen fundoplication in pediatric patients.
- It is important to recognize the signs and symptoms of early and late dumping syndrome in a timely manner to ensure timely diagnosis and management.

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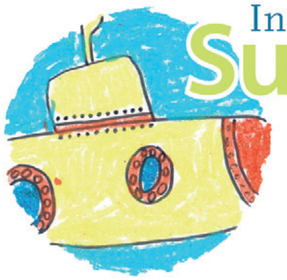

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5 A Very Tall 7-year-old Boy with Medulloblastoma

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AUTHOR DISCLOSURE Dr Rossfeld has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 7-year-old boy diagnosed 3 months earlier as having medulloblastoma and actively receiving chemotherapy is admitted to the oncology service for *Aspergillus* surgical site infection after tumor resection. He undergoes surgical debridement and is started on appropriate intravenous antifungal treatment, with a favorable clinical response. Although afebrile and clinically convalescing, lower extremity blood pressures (BPs) measured via automated electronic sphygmomanometer are persistently elevated (125–150/65–90 mm Hg), prompting a nephrology consultation.

Physical examination is notable for an irritable boy who is large for his age (height, 59.8 in [152 cm] [100th percentile]; and weight, 125.2 lb [56.8 kg] [100th percentile]), a manual upper extremity BP of 120/84 mm Hg, alopecia, and normal cardiopulmonary examination without peripheral edema.

Results of initial evaluation for causes of secondary hypertension, including urinalysis, serum chemistry/electrolytes/glucose, complete blood cell count, plasma renin activity, renal ultrasound, and echocardiogram, are normal. Additional history and evaluation reveal the diagnosis.

The Case Discussion, References, and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/1/41.

DISCUSSION

Attempting to reconcile BP readings by age, sex, and height, (1) it was realized that the patient's height exceeded the 95th percentile for age by 8.3 in (21 cm). His parents denied any growth spurt and reported that he had "always been heavy and tall." They had, however, noticed axillary and pubic hair as well as body odor for the preceding 5 months. His pediatrician was contacted, and a 1-year height velocity of 6.3 in (16 cm) was confirmed (mean for boys in the same age range is 2.2 in [5.5 cm]). Further evaluation was notable for 6-mL testes (Tanner stage II), bone age of 13 years (+6.6 SD), and, on early-morning measurement, elevated levels of total testosterone (22 ng/dL [0.76 nmol/L]; reference range for age, <2.5–10 ng/dL [<0.09–0.35 nmol/L]) and luteinizing hormone (LH) (0.63 mIU/mL [0.63 IU/L]; reference range for age, <0.2 mIU/mL [<0.2 IU/L]), whereas the follicle-stimulating hormone (FSH) level (0.87 mIU/mL [0.87 IU/L]) was within the reference range for age (<0.2–2.2 mIU/mL [<0.2–2.2 IU/L]). Brain magnetic resonance imaging demonstrated a normal pituitary gland, and the thyrotropin concentration was within the reference range. He was diagnosed as having central precocious puberty (CPP).

Central precocious puberty has been described in association with posterior fossa tumors. Despite a normal pituitary gland by magnetic resonance imaging, the proposed mechanism for CPP in this context is mass effect from the space-occupying lesion causing release of gonadotropin-releasing hormone (GnRH). For the one other case of CPP described specifically in association with medulloblastoma, (2) gonadotropins returned to prepubertal levels after tumor resection and chemotherapy/radiotherapy.

Having previously undergone tumor resection, this boy was administered leuprolide, which suppressed further pubertal changes. At follow-up 9 months after diagnosis of CPP, levels of LH (0.3 mIU/mL [0.3 IU/L]; reference range, 1.2–8.6 mIU/mL [1.2–8.6 IU/L]), FSH (1.3 mIU/mL [1.3 IU/L]; reference range, 1.3–19.3 mIU/mL [1.3–19.3 IU/L]), and testosterone (<0.1 ng/dL [<0.01 nmol/L]; reference range, 0.03–0.3 ng/dL [0–0.01 nmol/L]) were suppressed, and pituitary gland evaluation revealed thyrotropin, insulinlike growth factor-1, and insulinlike growth factor-binding protein 3 within their respective reference ranges. He has been taking amlodipine, with adequate BP control.

The Condition

Puberty is a nonspecific term that describes sexual maturation during adolescence. Puberty encompasses gonadarche—the maturation of the hypothalamic-pituitary-gonadal axis—and adrenarche—an independent but contemporaneous increase in adrenal production of androgens. The physiology of these processes is incompletely understood, but pulsatile GnRH is known to be imperative for gonadarche.

Our understanding of normally developing secondary sexual characteristics—as elucidated by Marshall and Tanner, (3)(4) the US Health Examination Survey, (5)(6) and more recently the Pediatric Research in Office Settings Network (7)(8) and NHANES III (9) data—suggests that the mean age at onset is 10.5 years for girls and 11.5 years for boys and follows an approximately normal distribution, with the SD being 1 year. A trend has been observed toward earlier onset for children of African American ethnicity and for girls compared with boys, but there has been no consensus to accept pubertal onset less than 2.5 SD below the mean age as normal. Puberty is, therefore, precocious if occurring before age 8 years in girls and 9 years in boys. In addition to early thelarche and pubarche, a height velocity consistently

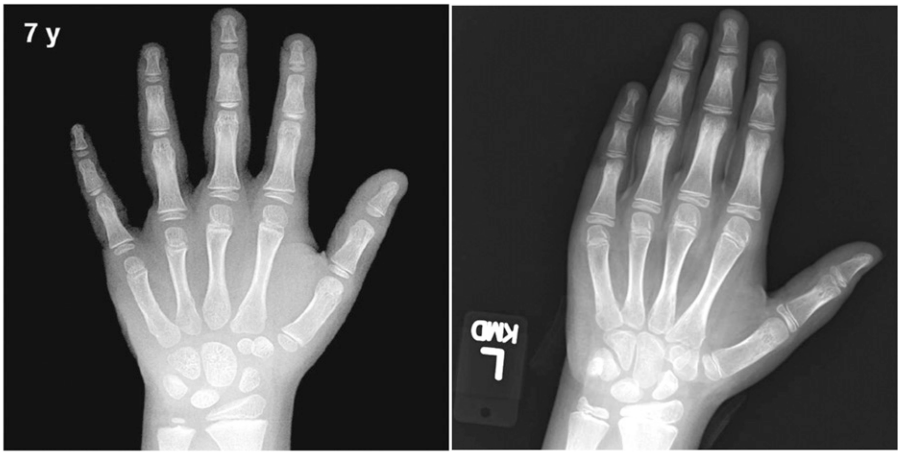

Figure. Bone age. Comparison with the reference image (left) reveals the 7-year-old patient (right) to have advanced bone age. Radiologic impression was bone age of 13 years (+6.6 SD). Reference image reproduced with permission from Gilsanz V, Ratib O. *Hand Bone Age: A Digital Atlas of Skeletal Maturity*. Heidelberg, Germany: Springer-Verlag Berlin; 2005.

above the 75th percentile warrants evaluation for precocious puberty.

The prevalence of precocious puberty is uncertain. Following the logic for a normal distribution, one would expect 2.5% of children to be affected. Available data, however, are discordant. A Danish registry–based study (10) reported the prevalence of a precocious puberty diagnosis of 0.2% for girls and less than 0.05% for boys. Meanwhile, a cross-sectional study of more than 17,000 girls across more than 25 states and Puerto Rico (7) reported stage 2 sexual maturation for 7-year-old girls at 6.7% and 27.2% prevalence for white and African American girls, respectively. Suggesting a trend toward earlier onset of puberty and racial differences, this study was limited by less than 10% of the study population being African American and visual inspection rather than palpation of breast tissue.

Differential Diagnosis

The differential diagnosis for suspected precocious puberty includes nonprogressive pubertal variants (ie, premature adrenarche, premature thelarche), CPP, and peripheral precocious puberty (PPP).

Nonprogressive variants of puberty may have isolated physical examination findings suggesting precocity and require serial monitoring to ensure continued absence of other secondary sex characteristics as well as normal bone age and height velocity.

Central precocious puberty represents activation of the hypothalamic-pituitary-gonadal axis and presents with the expected pubertal sequence, consistent with the child's biological sex, at an early age. Idiopathic causes predominate, but certain genetic causes are being elucidated. (11)(12) Other cases relate to an intracranial lesion or past cranial irradiation. Laboratory testing demonstrates pubertal LH and FSH levels that are suppressible by GnRH agonists.

Peripheral precocious puberty, in contrast, is independent of an active physiologic hormonal axis and manifests as a result of inappropriate exposure to sex hormones. This may occur from excess gonadal or adrenal sex hormone production, exposure to exogenous steroids, or, more rarely, germ cell tumors and may cause symptoms either consistent with or contrary to (eg, virilization of females) biological sex. In PPP, LH and FSH levels are suppressed and do not respond to stimulation by GnRH.

Management

The underlying etiology of precocious puberty drives its treatment. Primary causes, such as intracranial lesions or germ cell tumors, require targeted specialty care. For idiopathic causes of CPP, the decision to treat with GnRH agonists is based on the individualized need for delaying puberty, with attention to psychosocial issues and preservation of adult height. Treating PPP requires medical therapy to limit the production of (eg, finasteride, anastrozole) and/or response to (eg, spironolactone, tamoxifen, bicalutamide) excess sex hormones.

Lessons for the Clinician

- Hypertension now affects almost 5% of children, and secondary causes are present in 70% to 85% of affected patients younger than 12 years.
- Puberty is precocious if occurring before age 8 years in girls and 9 years in boys.
- In addition to early thelarche and pubarche, a height velocity consistently higher than the 75th percentile warrants evaluation for precocious puberty.

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Abdominal Pain in a Recently Immigrated 10-year-old Girl

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PRESENTATION

A 10-year-old previously healthy girl presents to the emergency department for evaluation of abdominal pain. Five days ago, she developed abdominal pain, which has been worsening. She has no history of fever, constipation, or diarrhea. She reports 4 episodes of nonbilious vomiting. There is no change in the color of her urine. She reports no other symptoms and denies any change in behavior. Her appetite and fluid intake are reported as increased, and she enjoys eating fast food every day. She has recently emigrated with her family from India to Canada. There is no significant family history of hemoglobinopathy or Wilson disease.

Physical examination reveals a weight of 118.4 lb (53.7 kg) (90th–97th percentile), height of 60.6 in (154 cm) (90th percentile), and BMI of 22.6 (90th–95th percentile). There is no evidence of hepatomegaly or jaundice. Abdominal examination reveals a soft abdomen with diffuse right upper quadrant tenderness and a negative Murphy sign.

Laboratory investigations reveal elevated aspartate aminotransferase (156 U/L [2.61 μkat/L]) and alanine aminotransferase (81 U/L [1.35 μkat/L]) enzyme levels, a normal amylase level (66 U/L [1.10 μkat/L]), and an elevated urobilinogen level (19.4 mg/24 h [33 μmol/d]). Her white blood cell count is elevated (17,100/μL [17.1×10^{9}/L]), with an increase in neutrophils (12,820/μL [12.82×10^{9}/L]). Her glucose level is within normal limits (109.9 mg/dL [6.1 mmol/L]), and she has a normal hemoglobin count (13.2 g/dL [132 g/L]). Hepatitis B surface antigen, heterophile antibody test, Epstein-Barr virus serology, and cytomegalovirus serology are negative.

Ultrasonography of the liver and gallbladder reveals a thin-walled gallbladder with multiple dependent, mobile, small gallstones. There are no findings suggesting perivesicular inflammation. The intrahepatic and extrahepatic bile ducts are not dilated or abnormal. There is no hepatic steatosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/1/42.

AUTHOR DISCLOSURE Ms Hudson and Dr Blake have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

Gallbladder disease is uncommon in the pediatric population. The most common presentation of biliary colic in the pediatric population is biliary dyskinesia, which is a motility disorder affecting the gallbladder with no evidence of gallstones. However, the presentation of biliary colic due to gallstones has been increasing in the pediatric population, which was seen in the patient presented herein. Historically, evidence of gallstones in children and adolescents has been most often associated with hemolytic disorders. However, the frequency of gallstones in the absence of a hemolytic disorder has recently been on the rise in the pediatric population and has been associated with a high BMI. The development of gallstones due to a diet high in fat and obesity is multifactorial and is thought to include a high secretion of cholesterol and poor gallbladder motility.

The adoption of westernized diets on immigration to Canada, including an increased consumption of readily available fast foods, can have a negative effect on the health of immigrants. After moving to a foreign country, factors such as a higher level of stress, children's preferences, and a lack of traditional foods can result in a diet that is higher in fat and sugar, with larger portions and more consumption of convenience food. South Asian immigrants in Canada have reported an increase in the consumption of convenience foods, sugar-sweetened beverages, and red meat, as well as an increase in eating meals outside the home at convenient food establishments. These changes in dietary habits may result in an increase in BMI, which is known to be a risk factor for pediatric gallstone formation. Insulin resistance has also been described as a dietary risk factor for gallstone formation in children.

Cholesterol gallstones (70%–100% cholesterol) contain a higher amount of cholesterol than can be broken down by micelles in bile. They are most often the result of hypersecretion of cholesterol due to excess dietary intake and resulting increased hepatic uptake. Fat-rich food intake has also been identified as a risk factor for recurrence of gallstones.

Biliary colic is the most common symptom of gallstones, predominantly in the right upper quadrant of the abdomen. This biliary colic is often accompanied by nausea and vomiting. Nonspecific abdominal pain and irritability may be the only presenting symptoms, particularly in children younger than 5 years. Patients can present with cholangitis, choledocholithiasis, or pancreatitis, which is often accompanied by pain, fever, and jaundice. Gallstones may also be asymptomatic, in which case they are incidentally detected by ultrasonography.

Evaluation for suspected gallstone disease includes liver biochemistry as hepatic, alanine, and aspartate aminotransferase levels, which are elevated early on in the obstruction. Serum bilirubin, alkaline phosphatase, and γ-glutamyl transferase levels elevate later in the course. A complete blood cell count often reveals a nonspecific elevated white blood cell count. Amylase levels are elevated when the patient has pancreatitis. Another important investigation in the diagnosis of gallstones is transabdominal ultrasonography, which can reveal gallstones, hepatobiliary duct dilatation, and pancreatitis. Suspicion of congenital ductal anomalies may be investigated best using magnetic or endoscopic retrograde cholangiopancreatography.

Management

Laparoscopic cholecystectomy is a safe and effective treatment option for biliary colic and gallbladder disease in the pediatric population. Furthermore, new evidence suggests that a same-day discharge after laparoscopic cholecystectomy is safe for pediatric patients, just as it is for adults. Cholecystectomy still remains an uncommon surgical procedure in the pediatric population; however, it is often performed in young female adolescents who are overweight or obese and have multiple gallstones. Resolution or improvement of preoperative symptoms after a laparoscopic cholecystectomy has been reported to be as high as 92.6% of patients undergoing the procedure. Complications of the procedure that were reported by a recent study include a prolonged ileus, wound infection, and the requirement for an incisional hernia repair. Comparison between same-day discharge and overnight hospital stay after the procedure found no differences in the complication rate, readmission, or follow-up before the scheduled appointment.

Patient Course

The patient is discharged from the emergency department on a 5-day course of a histamine-2 blocker (ranitidine), with outpatient follow-up arranged with a pediatric general surgeon. Repeated laboratory investigations 1 month later reveal that the previously elevated liver enzyme levels and white blood cell count have returned to normal. She is instructed to decrease the fat content of her diet, and an elective laparoscopic cholecystectomy is arranged.

Lessons for the Clinician

- Clinicians should be aware of the difficulty of dietary acculturation for newly immigrated patients.
- Preventive efforts should be made to provide education about healthy food choices and the danger of replacing fruits and vegetables with more convenient fast food.
- Newly immigrated children and adolescents may face negative health consequences that are not usually present in the pediatric population.

- Biliary colic and gallbladder disease should be considered with a presentation of right upper quadrant abdominal pain and raised liver enzyme levels.

Suggested Readings

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Medication Treatment of Adolescent Opioid Use Disorder in Primary Care

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Medication-Assisted Treatment of Adolescents With Opioid Use Disorders. Committee on Substance Use and Prevention. *Pediatrics.* 2016;138(3). Available at: https://doi.org/10.1542/peds.2016-1893

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Monitoring the Future National Survey Results on Drug Use, 1975-2016: Overview, Key Findings on Adolescent Drug Use. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. Ann Arbor, MI: Institute for Social Research, The University of Michigan; 2017.

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Receipt of Services for Behavioral Health Problems: Results from the 2014 National Survey on Drug Use and Health (National Survey on Drug Use and Health [NSDUH] Data Review). Han B, Hedden SL, Lipari R, Copello EAP, Kroutil LK. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FRR3-2014/NSDUH-DR-FRR3-2014/NSDUH-DR-FRR3-2014.pdf. Published September 2015

Since 2000, a threefold increase in unintentional opioid poisonings among adolescents has followed a dramatic increase in adult opioid-related deaths. In 2016, 1 in 13 high school seniors reported past-year nonprescription use of opioids. Despite these increases, only 8.5% of adolescents received addiction treatment.

In September 2016, the American Academy of Pediatrics (AAP) released a policy statement recommending that pediatricians offer medication for the treatment of severe opioid use disorder (OUD). There are 3 medications approved for OUD treatment: buprenorphine, naltrexone, and methadone. Buprenorphine and methadone are opioid agonists that decrease cravings for opioids and treat withdrawal symptoms. In addition, both provide opioid blockade, which means that if an individual uses another opioid after taking their medication, euphoric effects are blocked. Naltrexone, an opioid antagonist, blocks the opioid receptor, preventing the effects of opioid use. It may also reduce cravings for opioids. Head-to-head clinical trials of these medications in adolescents are lacking; observational data from adults suggest that of these medications, methadone may be the most effective for retention in treatment.

MEDICATIONS

Buprenorphine is taken daily via sublingual tablets or films and can be prescribed in pediatric primary care. The film is a dissolving strip absorbed through the buccal mucosa or tongue. Buprenorphine has 2 formulations: 1) combined with naloxone (buprenorphine/naloxone) and 2) a formulation without naloxone. Pediatricians should prescribe the combined formulation. Naloxone is not absorbed systemically, but if misused and injected, naloxone binds to block the opioid receptor, triggering uncomfortable withdrawal symptoms that discourage misuse. Pregnant females are generally prescribed buprenorphine only due to concerns about fetal naloxone exposure. Per federal regulations, providers must complete an 8-hour online or in-person course to receive a US Drug Enforcement Agency waiver before prescribing buprenorphine. As of 2016, nurse practitioners and physician assistants can also obtain waivers. Multiple organizations, including the AAP, have endorsed an adolescent-focused version of the course for pediatricians (http://www.aap.org/mat).

Naltrexone is available in a daily oral tablet or a monthly depot injection. No special certification is required to prescribe naltrexone. Many practitioners initially prescribe tablets for 1 week to ensure tolerability before transitioning to monthly injection. Because naltrexone is an opioid antagonist, it can precipitate sudden withdrawal symptoms in a patient who recently used opioids. Therefore, clinicians should only administer naltrexone 3 to 6 days after the most recent use of short-acting opioids (eg, most short-acting prescription opioids or heroin) and 7 to 10 days after the most recent use of long-acting opioids (eg, most long-acting prescription opioids, buprenorphine, or methadone). It is important to check the results of a urine drug test (UDT) before starting naltrexone and to observe the first oral dose in the clinic to monitor (~60 minutes) for signs of withdrawal. Generally, naltrexone is not used in pregnant women, and if a patient taking naltrexone becomes pregnant, an addiction specialist should be consulted.

Methadone is a full opioid agonist. The US federal regulations mandate dispensing methadone in federally certified opioid treatment programs, and there are strict guidelines about when a minor can qualify for treatment. As a result, it is uncommonly used to treat adolescent patients in the United States.

TREATMENT PROTOCOL

Amidst a shortage of treatment options for adolescents in many settings (eg, rural settings), pediatric primary care practices can provide effective care even without extensive resources. Due to strict federal regulations about methadone dispensing, pediatricians will generally be restricted to prescribing buprenorphine, buprenorphine/naloxone, and naltrexone in their practice, which are the treatment models that we further describe herein. At minimum, practices should establish a clinical model that includes a pediatrician who prescribes medication and monitors treatment and a mental health practitioner who provides behavioral therapy.

After referral to treatment, the patient should undergo an assessment for OUD based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria. Whether a teen can consent to his or her own substance use treatment without a parent differs across states; practitioners should become familiar with regulations in their jurisdictions and should adhere to federal statutes. Before starting medication, the patient, family, and clinician should also sign a treatment agreement. The agreement outlines expectations related to visit adherence, conduct in the clinic, participation in routine UDT, and receipt of behavioral health counseling (including, eg, motivational enhancement therapy, cognitive behavioral therapy, and adolescent community reinforcement approach).

Laboratory tests are ordered and immunizations are reviewed for all patients to ensure receipt of hepatitis A and B vaccines or immunity (Table). Naltrexone should not be offered to patients with liver function test results of 3 times the upper limit of normal or greater. In those cases, clinicians should monitor liver function tests, determine the etiology of the increase, and reconsider initiating naltrexone

TABLE. Medication Initiation Checklist for Treatment of Severe Opioid Use Disorder

At the first visit	Review of confidentiality
	Opioid use disorder assessment and diagnosis
	Assessment of other substance use disorders, including tobacco use disorder
	Discussion of treatment options
	Laboratory tests
	  Complete blood cell count
	  Chemistry
	  Liver function
	  Human immunodeficiency virus
	  Syphilis
	  Hepatitis panel (hepatitis A and C antibodies, hepatitis B surface antibody and surface antigen)
	Gonorrhea/chlamydia culture
	– For females: urine pregnancy test
	– Vaccinations[a]
	  ○ Hepatitis A
	  ○ Hepatitis B
	– Sign release to obtain information about previous treatment
	– Prescription for naloxone

If medication therapy is indicated, before medication initiation	– Sign the treatment agreement and consent form – Assess for co-occurring mental health disorders – Refer to behavioral health (or offer within program) – Discuss safe medication storage planning – Review urine drug testing expectations and visit frequency

[a] *Confirm hepatitis A and B virus immunity before vaccinating.*

therapy at a later date if possible. Safe medication storage is reviewed with patients and caregivers, including encouraging storing medication in a lockbox. If possible, caregivers should be asked to observe all medication administrations. If there are small children in the home, caregivers should be given additional guidance about avoiding unintentional ingestion, particularly for buprenorphine.

In addition, UDT is implemented weekly for 6 weeks, then biweekly for 6 weeks, and then monthly if the patient is stable. The UDTs have 2 purposes: 1) to monitor for opioid or other polysubstance use, including use of benzodiazepines, which greatly increases the risk of overdose; and 2) to monitor medication adherence with buprenorphine (because buprenorphine and its metabolites can be detected in the urine). Urine drug panels should include testing for opiates, cocaine, amphetamines, benzodiazepines, and barbiturates, as well as expanded panel testing for oxycodone, methadone, buprenorphine, and fentanyl opioids.

Providers should also assess for co-occurring disorders and provide behavioral health supports and referrals to psychiatry when needed. Overdose education and a naloxone prescription should be offered to all patients and families.

Generally, reimbursement rates are standard for primary care–based medical visits when treating OUD. However, insurance companies may cover a limited number of UDTs, and checking with them regarding coverage is important.

CONCLUSION

In the midst of an opioid overdose crisis, pediatricians are uniquely positioned to offer early treatment with medications for severe OUD. Throughout the United States (particularly rural settings), subspecialty drug treatment is not available or is impractical due to distance for many families; pediatric providers may be the only providers available to offer evidence-based addiction care. Pediatricians' focus on prevention coupled with their longstanding relationships with their patients and families provide the ideal opportunity to intervene, provide treatment, and potentially prevent the consequences of long-term OUD.

NOTE. The views expressed are those of the authors and do not reflect the official policy of the National Institutes of Health or the US government.

COMMENT: Our country is currently experiencing an epidemic of morbidity from opioid use, addiction, unintentional ingestion, suicide attempts, and death. One reference noted the death toll from the September 11 attacks to be comparable with the number of deaths from opioid use every 3 weeks. Adolescents are at high risk, and deaths from opioid overdose increased sixfold from 1999 to 2010 in 15- to 24-year-olds. The morbidity from opioid overdose may occur from ingestion of their own prescriptions or those of family or friends. Federal and statewide interventions are needed. In addition to patients with whom I have been involved who experienced opioid addiction, I have cared for 2 patients in the past 2 years who experienced methadone ingestion that was a family member's medication. One was a 17-year-old boy who took his grandmother's methadone to a party and ingested it for recreational use. Unfortunately, when he was found unresponsive, his friends thought he was "sleeping it off," which resulted in him not getting medical assistance until after he had experienced permanent anoxic brain injury. Another patient was an 18-month-old girl admitted for croup and respiratory support. A few hours after hospitalization her parents received a telephone call from her grandmother stating that she now recalled that the patient had licked the cap of her methadone bottle. On reevaluation, this toddler now had pinpoint pupils and evolving evidence of respiratory depression requiring naloxone hydrochloride therapy. Hence, this reinforces the importance of counseling regarding safe storage of treatment medications in the home.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/ages-stages/teen/substance-abuse/Pages/The-Opioid-Epidemic.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

Contiguous Gene Syndromes

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AUTHOR DISCLOSURE Drs Pereira and Marion have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The term *contiguous gene syndromes* describes a group of disorders in which a small deletion or duplication of genetic material that contains multiple genes causes a recognizable phenotype. Because microarrays capable of identifying microdeletions and microduplications have become a first-tier genetic test for patients with multiple congenital anomalies, intellectual disabilities, and autism spectrum disorder, more contiguous gene syndromes have been identified. Among the more common of these disorders are Prader-Willi syndrome (PWS), Angelman syndrome (AS), and Williams syndrome (WS). Another disorder, 22q11.2 deletion syndrome, was discussed in a recent *In Brief*. The accompanying Table is a compilation of known contiguous gene syndromes.

Although markedly different in phenotype, PWS and AS are both associated with chromosome 15 microdeletions. Prader-Willi syndrome has a prevalence of 1 in 10,000 to 30,000. In infancy, children with PWS have severe hypotonia, which leads to difficulty with feeding, failure to gain weight, and often the need for nasogastric or gastrostomy tube feeding. By 9 to 18 months, muscle tone begins to improve, and affected children are able to eat without assistance; in fact, they develop insatiable appetites. If untreated, this hyperphagia leads to multiple medical complications: obesity, type 2 diabetes mellitus, and obstructive sleep apnea. With age, facial features characteristic of PWS become more evident, including almond-shaped eyes, thin upper lip, downturned mouth, and narrow bifrontal head diameter. Generalized hypothalamic-hypopituitary axis insufficiency commonly occurs, affecting growth hormone secretion, thermoregulation, thyroid function, and respiratory control. Hypogonadism affects most patients, manifesting as cryptorchidism in males, incomplete pubertal development, and infertility. Behavioral and developmental problems include perseverant speech and obsessive compulsive behavior, with temper tantrums (usually focused on securing food), skin picking, and stubbornness. Intellectual disabilities include cognitive deficits with sparing of personal-social skills; mean IQ is usually in the 60 to 70 range.

In contrast, AS, with a prevalence of 1 in 12,000 to 24,000, is usually not noticed at birth. However, during the child's first year after birth, delays in the achievement of developmental milestones become obvious, as hyperkinetic, uncoordinated, ataxic movements of the trunk and limbs prevent the child from being able to sit, stand, and walk without assistance. Children with AS usually do not walk until 3 or 4 years of age, and ataxia makes their gait unsteady. Most affected children never attain language, remaining nonverbal. Receptive communication is better than expressive. Children with AS develop acquired microcephaly. Seizures occur at some time in nearly all children, and they are usually present by age 3 years. Excessive drooling and oral behaviors can also be seen. Soon after the condition was described by Dr Harry Angelman

American Academy of Pediatrics: Health Care Supervision for Children with Williams Syndrome. Committee on Genetics. *Pediatrics.* 2001;107(5):1192–1204

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Prader-Willi Syndrome. Cassidy SB, Schwartz S, Miller JL, et al. *Genet Med.* 2012;14(1):10–26

Prader-Willi, Angelman, and 15q11-q13 Duplication Syndromes. Kalsner L, Chamberlain SJ. *Pediatr Clin North Am.* 2015;62(3):587–606

TABLE. **Clinically Recognizable Contiguous Gene Syndromes**

NAME	DESCRIPTION
Deletions	
1p36	Facial features (midface retrusion, deep set eyes, straight eyebrows, pointed chin, microbrachycephaly, low set ears), developmental delay, hypotonia, congenital heart defects, structural brain anomalies
2q37	Developmental delays, obesity, short stature, brachymesophalangy especially of the fourth digit
4p- (Wolf-Hirschhorn)	Facial features (microcephaly, high anterior hairline, wide-spaced eyes, wide nose bridge, high-arched palate, micrognathia, downturned mouth), developmental delay, intellectual disability, seizures, skeletal abnormalities, congenital heart anomalies
5p- (cri du chat)	High-pitched cry, microcephaly, hypertelorism, low set ears, developmental delay, intellectual disability, hypotonia
7q11.23 (Williams)	Refer to text
9q22.3	Developmental delay, intellectual disability, macrosomia, seizures, metopic craniosynostosis, hydrocephalus (obstructive); also includes features seen in Gorlin syndrome (*PTCH1* gene in this microdeletion)
11p (WAGR)	Wilms tumor, aniridia, intellectual disability, renal anomalies, genitourinary abnormalities
15q11.2-q13 (Angelman)	Refer to text
15q11.2-q13 (Prader-Willi)	Refer to text
15q24	Facial features (high anterior hairline, hypertelorism, downward-slanting palpebral fissures, broad nasal bridge, smooth philtrum), growth retardation, global developmental delay, intellectual disability, extremity malformations, eye abnormality, genital abnormality
16p11.2	Intellectual disability, developmental delay, macrocephaly, structural brain abnormalities, vertebral anomalies
17p13.3 (Miller-Dieker)	Lissencephaly causing intellectual disability, developmental delay, spasticity, and seizures
22q11.2	Cardiac abnormalities, cleft palate/pharyngeal insufficiency, immunologic problems, learning issues, hypocalcemia, psychiatric issues
Duplications	
7q11.23	Facial features (macrocephaly, deep set eyes, upper lip has thin vermilion border, high-arched palate), neurologic changes, cardiovascular disease, behavioral issues, developmental delay

in 1965, the term *happy puppet syndrome* was coined to describe the features of the condition: the ataxic, jerky gait was said to resemble the movements of a puppet on a string, and the children were thought to be happy because they often smile and laugh even without apparent reason. The term is now considered pejorative and is no longer acceptable.

Both PWS and AS are associated with a microdeletion of approximately 20 genes in chromosome 15q11.2-q13. Some genes in this cluster show imprinting because of epigenetic changes: they are expressed in the chromosome inherited from only 1 parent. In the PWS/AS critical region, the *SNRPN* gene is expressed only in the paternally inherited chromosome 15, and the *UBE3* gene is expressed only in the maternally inherited chromosome. Prader-Willi syndrome results from a deficiency of the *SNRPN* gene product: if no paternally inherited copy of *SNRPN* is present, the child develops PWS. There are 3 ways in which failure to express *SNRPN* can occur:

(1) A microdeletion of the paternal chromosome 15q11.2 critical region (seen in 70% of patients).

(2) Inheritance of 2 copies of the mother's chromosome 15 and no copy of the father's chromosome 15 (25%–30% of patients). This phenomenon, called maternal uniparental disomy, probably results from trisomic rescue, in which the conceptus begins with trisomy 15 (from the presence of an extra copy of the mother's chromosome 15). Because trisomy 15 is prenatally lethal, the embryo is "rescued" by the spontaneous loss of 1 of the 3 copies of chromosome 15; if the loss occurs to the father's chromosome 15, the result is that the embryo has 2 copies of maternal 15q11.2 and, therefore, no expressed copy of *SNRPN*.

(3) An abnormality in the imprinting center, the region of chromosome 15 that houses the instructions for *SNRPN* silencing or expression (up to 5% of patients), so that expression does not occur properly.

The PWS phenotype is variable. Larger deletions lead to lower intellectual capabilities and more behavioral/psychological problems. Prader-Willi syndrome caused by maternal uniparental disomy is associated with less striking physical features and better verbal intelligence, but with a higher risk of psychosis. Current research is focused on *SNORD* genes, other genes in the PWS/AS critical region, and their effects on the PWS phenotype.

Angelman syndrome results from lack of expression of the *UBE3A* gene, the only maternally expressed gene in the PWS/AS critical region, although other genes may play a role in phenotypic variations. As in PWS, 3 scenarios can lead to AS:

(1) A microdeletion of the maternally inherited chromosome 15q11.2-q11.3 (~65% of patients).
(2) Paternal uniparental disomy (~8% of patients).
(3) An error in the imprinting center (~3% of patients).

Methylation studies can detect more than 99% of PWS cases and approximately 80% of AS cases; when AS is still suspected even after a negative methylation study, sequencing the *UBE3A* gene would be reasonable (11% of patients). In most patients, the methylation or deletion defect in PWS or AS is a de novo event, but rare cases have been reported in which a mother with PWS bore a child with AS.

Williams syndrome is another contiguous gene syndrome in which a microdeletion leads to a recognizable pattern of malformations, with a prevalence of 1 in 7,500 to 10,000. The WS critical region on chromosome 7q11.23 contains 25 to 30 genes. Individuals with WS have mild intrauterine growth restriction, with a birthweight usually less than 3,402 g. Early in life, infants tend to have poor feeding, failure to thrive, and are irritable and colicky; they are noted to have a low-pitched, "gravelly" cry. Their distinctive facial phenotype in the past has been described as elfin-like, characterized by bitemporal narrowing, prominence of the ears, a long philtrum, periorbital puffiness, a short nose, a wide mouth, and full lips. The irides are often blue, with a stellate pattern of pigment.

Cardiac anomalies occur in approximately 80% of individuals with WS and are quite distinctive. Stenosis of any blood vessel can occur, and narrowing tends to be progressive. The lesion most characteristic of WS is supravalvular aortic stenosis, seen in approximately 67% of affected children. Supravalvular pulmonic stenosis may also occur, often being diagnosed before the aortic stenosis. Stenosis of the renal arteries often causes substantial hypertension, and coronary artery stenosis can be associated with myocardial infarction and sudden death. An array of other congenital heart lesions can also be seen, including ventricular septal and atrial septal defects.

Endocrine abnormalities are also common and include hypothyroidism and idiopathic hypercalcemia (the latter is seen in 20% of patients). Eighty percent of children with WS develop early puberty. Because children with WS grow at a different rate from other children, special height and weight growth charts are available for them.

Individuals with WS often have a distinctive personality. Described as loquacious and outgoing, the typical patient with WS has well-developed personal-social skills. However, cognitive skills are substantially impaired, with an average IQ of approximately 56; verbal IQ score tends to be higher than visuospatial construction score, with verbal memory better than spatial memory. Early in life, hypotonia is common, but it improves with time; by late childhood, hypertonia with joint contractures may develop.

As in most contiguous gene syndromes, the correlation between the deleted genes and the phenotype is still being elucidated. For WS, the *ELN* gene, which encodes a connective tissue protein that gives elasticity to medium-large arteries and skin, could result in the cardiovascular issues seen in the syndrome. It is still unclear which genes are associated with the intellectual disability. As in PWS and AS, most cases of WS arise from a de novo microdeletion. Because this is an autosomal dominant disorder, each child born to an individual with WS has a 50% chance of inheriting the deletion and, thereby, manifesting the disorder.

For all the syndromes described herein, health-care management and supervision revolve around treating the presenting symptoms, with published guidelines available for PWS and WS. Because multiple organ systems can be affected in these syndromes, coordinated care with an interdisciplinary approach among the primary care provider and the subspecialty providers is critical. Creating a strong medical home for patients with contiguous gene syndromes helps improve their quality of life.

COMMENT: Drs Pereira and Marion mention methylation studies as a means of detecting PWS and AS. Methylation is an epigenetic phenomenon in which methyl (CH_3) groups attach to DNA, functioning to modify gene expression. Typically, when methyl groups attach to a gene promoter, methylation signals shut down, turning off gene transcription. When methylation suppresses a gene in 1 parent, called *imprinting,* the only active allele of that gene inherited by a child comes from the other parent. Methylation testing can determine whether the critical genetic region under investigation is maternally inherited, with one of the father's genes in the region turned off (PWS), or is paternally inherited, with 1 of the mother's genes inactivated (AS).

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR JANUARY 2018 PEDIATRICS IN REVIEW

Urinary Tract Infections in Children: 1. E; 2. B; 3. B; 4. C; 5. B.

Preparing Your Pediatric Patients and Their Families for the Operating Room: Reducing Fear of the Unknown: 1. C; 2. D; 3. B; 4. E; 5. E.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone and Hyponatremia: 1. C; 2. D; 3. E; 4. C; 5. E.

Pediatric Imaging: Radiation Exposure and How We Image

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AUTHOR DISCLOSURE Dr Levin has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

During the past decade, technological advances have improved the accessibility, accuracy, and speed of medical imaging. This is particularly true of the newest computed tomography (CT) scanners equipped with multirow detectors that provide exceptional diagnostic accuracy and capture multiple images in seconds, obviating the need for patient sedation. These advances, although resulting in significantly improved diagnostic benefits, have led to a rapid increase in CT scanning, particularly in children. In the United States, CT contributes to half of all medical radiation exposures; pediatric CT scans compose 10% of all CT scans.

Although the benefits of CT are significant, debate is ongoing about potential risks posed by the low-level radiation exposure associated with CT, especially in children. Children may be particularly susceptible to developing cancer because of the increased radiosensitivity of their growing organs and their long expected life spans. However, the risk from exposure to low-level radiation is uncertain, and the dose actually delivered by CT is estimated. Furthermore, the estimates of risk for cancers related to radiation are based on extrapolation from studies of atomic bomb survivors who received substantially higher doses of radiation than those used in medical imaging. Nevertheless, techniques to significantly reduce the dose of radiation from CT have been implemented.

A variety of imaging modalities are available to the radiologist: radiography, fluoroscopy, nuclear scintigraphy, CT, and positron emission tomography (PET) use ionizing radiation; and magnetic resonance (MR) imaging and ultrasonography do not. The choice of modality can be confusing. Some examinations optimize anatomic detail or are complementary when used in conjunction with another modality. Others provide functional data or offer unique information not provided by other imaging modalities. The ideal modality differs with each patient and reflects the diagnostic question being asked and the patient's clinical condition, specifically, the child's tolerance for a specific modality. When feasible, use of MR or ultrasonography is preferable in children. However, CT and other modalities that use ionizing radiation should not be avoided when indicated. In some patients, CT scanning is simply the best choice given the information sought by the clinician. Discussion with the pediatric radiologist optimizes and individualizes the choice of imaging.

Whenever possible, ultrasonography should be used in the imaging of children. Ultrasonography is readily available, portable, requires no sedation, and imposes no ionizing radiation. The small body habitus of children is ideal for ultrasonography, and the development of high-frequency pediatric probes allows for scanning at various depths. Ultrasonography is the optimal initial examination to evaluate the hepatobiliary and genitourinary systems. If additional imaging is required, MR cholangiography, MR urography, or pelvic MR may be obtained. The diagnosis of intussusception is best made using ultrasonography. Similarly, ultrasonography is the initial examination in cooperative children with suspected

Ten Steps You Can Take to Optimize Image Quality and Lower CT Dose for Pediatric Patients. Strauss KJ, Goske MJ, Kaste SC, et al. *Am J Roentgenol.* 2010;194(4):868–873. doi:10.2214/AJR.09.4091

CT Dose and Risk Estimates in Children. Frush DP. *Pediatr Radiol.* 2011;41(suppl 2): S483–S487. doi:10.1007/s00247-011-2098-z

Update on Radiation Safety and Dose Reduction in Pediatric Neuroradiology. Mahesh M. *Pediatr Radiol.* 2015;45(suppl 3): S370–S374. doi:10.1007/s00247-015-3379-8

Anesthesia and Developing Brains: Implications of the FDA Warning. Andropoulos DB, Greene MF. *N Engl J Med.* 2017;376(10):905–907. doi:10.1056/NEJMp1700196

appendicitis. Ultrasonography of the head, routinely performed in the NICU, readily demonstrates intracranial hemorrhage, ischemia, or structural abnormalities. In infants younger than 6 months, acetabular anatomy and hip position with and without stress can be dynamically assessed with ultrasonography. Similarly, in suspected pyloric stenosis, ultrasonography can distinguish the transient findings of pylorospasm from true pyloric muscle thickening. Doppler imaging allows assessment of the degree, direction, and velocity of vascular flow, as well as systolic and diastolic flow patterns. Advances in Doppler technology now provide exquisite vascular anatomic detail. New ultrasonography techniques promise added benefits and include 3-dimensional imaging, elastography (useful for solid tumors, liver fibrosis, etc), and microbubble ultrasonography contrast agents. Limitations include the presence of air (limited use in assessing the lungs) and bone.

Magnetic resonance imaging also imparts no ionizing radiation. It is the study of choice in evaluating congenital heart disease after echocardiography, the central nervous system, and the musculoskeletal system. Cardiac MR provides anatomic and functional information. In the brain it provides superior assessment of the parenchyma than does CT and is the optimal examination in a child with seizures or developmental delay. In children with ventriculoperitoneal shunts, both the degree of hydrocephalus and shunt location are well assessed with MR. Low-dose CT scan protocols for ventriculoperitoneal shunt assessment are the alternative for children unable to undergo MR. In the musculoskeletal system, MR provides unique information about marrow disease. With intravenous contrast, MR is indicated for suspected osteomyelitis and in the evaluation of bone tumors. In addition, it is the modality of choice in assessing joints and soft tissues in inflammatory conditions or after trauma. MR has replaced the fluoroscopic small bowel follow-through in the evaluation of inflammatory bowel disease and is increasingly used in the diagnosis of appendicitis: fast MR protocols are available to rapidly define abdominal and pelvic fluid collections in children with ruptured appendicitis. Magnetic resonance urography and cholangiography provide anatomic and functional assessment of the urinary and hepatobiliary systems. However, MR examinations are costly, limited in availability, and lengthy, requiring the patient to remain still for a prolonged period of time. In young children, sedation is often necessary. When sedation is contraindicated, CT serves as the best alternative to MR.

The rapidity of CT imaging makes it the preferred modality for children who cannot hold their breath or remain still without sedation. Given recent publications on the adverse effect of anesthesia on brain development in young children and infants, CT provides an alternative, fast, and efficient method of imaging without sedation. In addition, CT is effective in unstable patients for whom sedation is not possible or those with a contraindication to MR.

Contrast-enhanced CT scanning is the study of choice in trauma. It rapidly provides detailed information about central nervous system, solid organ, and vascular injury as well as the presence of a pneumothorax or pneumoperitoneum. Abdominal ultrasonography is insufficient in assessing abdominal or pelvic injury; a normal ultrasonography finding does not exclude solid organ or bowel injury. Evaluation of lung parenchyma for entities such as interstitial disease, congenital lung lesions, pulmonary infections, nodules, or masses requires chest CT—no other imaging modality allows detailed evaluation of the lung parenchyma.

Radiation exposure from fluoroscopy depends on the dose parameters, duration of the study, patient size, and use of appropriate shielding and coning of the fluoroscopic beam. Initiatives to reduce the dose of fluoroscopic radiation have been effective. Fluoroscopy remains the modality of choice to evaluate the gastrointestinal tract in infants and young children. Although ultrasonography has been proposed to replace fluoroscopy when malrotation or volvulus is suspected, most pediatric radiologists continue to perform fluoroscopic upper gastrointestinal tract series. Similarly, fluoroscopic guidance generally remains the modality of choice for air reduction of an intussusception. Contrast enemas for functional and structural distal bowel obstruction in infants remain the diagnostic imaging modality of choice. With the development of microbubble ultrasonography contrast, fluoroscopic voiding cystograms, which evaluate bladder and urethral anatomy and assesses for vesicoureteral reflux, may be replaced by ultrasonography in the future.

The correct imaging modality is the one that provides the most accurate answer to the clinical question at hand in the quickest, safest, and easiest manner for the individual patient. In all instances, whenever possible, discussion with dedicated pediatric radiologists who subscribe to the As Low As Reasonably Achievable (ALARA) principle and to the American College of Radiology Appropriateness Criteria is encouraged. Discussions between pediatricians and their pediatric radiology colleagues serve to guide the pediatrician in selecting the best imaging modality for each patient, eliminate potentially unnecessary studies, and reduce radiation exposure. The potential risks of medical radiation must be weighed against the diagnostic benefits of imaging.

COMMENT: For those of us who grew up in the era of radiography and fluoroscopy, the variety of imaging choices now available is astonishing and, for many of us, confusing. I could not have been more relieved to see CT scanning replace the horror of pneumoencephalography, even if my first experience with CT came as a medical student on an elective in neurology, when the resident I was accompanying explained to a woman in her 60s that she would be going for a new diagnostic test that would "take cuts of your brain!" I could see in her panicked eyes the picture of a deli slicing machine. Then came ultrasound, all kinds of scintigraphy, MR imaging, and PET scans, and each modality over time has become more sophisticated, with its own expanding set of bells and whistles. Add to the complexity of the choice among so many modalities the issues of exposure to radiation (especially for children) and the possible need for sedation (again, especially for children), and clearly the knowledgeable pediatric radiologist has a major role to play in guiding our choices.

Another consideration entirely is how many of the imaging studies we order are really necessary. Aside from the worry about potential litigation if enough tests are not ordered, economic pressures come into play. Scanners are expensive, and once purchased, whether by hospitals or imaging practices, can only be paid for when they are used, and so they are used and used and used. Sometimes, probably often, overused.

– Henry M. Adam, MD
Associate Editor, *In Brief*

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- https://www.healthychildren.org/English/health-issues/conditions/treatments/Pages/Imaging-Tests.aspx

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in Brief

Guillain-Barré Syndrome

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AUTHOR DISCLOSURE Drs Chung and Deimling have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Guillain-Barré syndrome (GBS) is a peripheral nervous system disorder that presents as a rapidly progressive, ascending, flaccid paralysis with diminished or absent reflexes. The disease is often triggered by an infectious process, and it affects children of all ages. Once considered a single disease, many subtypes have been identified based on the neuronal components involved. Important subtypes to consider include acute inflammatory demyelinating polyradiculoneuropathy, which targets segments of the myelin sheath. Other subtypes include acute motor axonal neuropathy and acute motor and sensory axonal neuropathy, both of which target the neuronal axon. Miller Fisher syndrome (ataxia, areflexia, and ophthalmoplegia) falls under the GBS categorization as well, although it usually involves minimal to no weakness. With the eradication of poliomyelitis in the developed world, GBS is now the most common cause of acute flaccid paralysis in infants and children, although still rare in children younger than 2 years. The incidence in Western countries ranges from 0.89 to 1.89 cases per 100,000 person-years. With every 10-year period after the first decade after birth, there is a 20% increase in incidence, with males more affected than females.

Although poorly understood, the mechanism of GBS is likely related to an immune-mediated trigger, such as an infection, that affects peripheral nerve components due to molecular mimicry. Classically, this trigger is a gastrointestinal or upper respiratory tract illness within 4 weeks of presentation. Possible viral agents include cytomegalovirus, Epstein-Barr virus, influenza, and human immunodeficiency virus, and bacterial triggers include *Mycoplasma*, *Haemophilis*, and, most commonly, *Campylobacter jejuni*, which accounts for 20% to 30% of US and European cases. Although rare, vaccination, surgery, trauma, transplant, lymphoma, and systemic lupus erythematosus have also been associated with GBS.

The differential diagnosis of the presenting features of GBS (flaccid paralysis, areflexia, or a combination) is extensive and may include pathology of the cerebellum, spinal cord, peripheral nerves, and musculature. Conditions that may have similar features include acute cerebellar ataxia, transverse myelitis, spinal cord compression, poliomyelitis, tick-borne paralysis, myasthenia gravis, myositis, and additional myopathies. Guillain-Barré syndrome is a clinical diagnosis, and progressive motor weakness of more than 1 limb and areflexia or marked hyporeflexia are required. Features strongly supporting the diagnosis include progression of onset over several days to less than 4 weeks, symmetrical involvement, painful onset, mild/absent sensory symptoms, cranial nerve involvement, autonomic dysfunction, absence of fever, and recovery 2 to 4 weeks after the onset of peak or plateauing of symptoms. The most useful diagnostic tests are cerebrospinal fluid (CSF) studies, electromyography, and, less specifically, magnetic resonance imaging (MRI). Classic CSF findings show an elevated protein level (albuminocytologic dissociation), along with a normal cell count with

Guillain-Barré Syndrome. Yuki N, Hartung HP. *N Engl J Med.* 2012;366(24):2294–2304

Guillain-Barré Syndrome. Hughes RA, Cornblath DR. *Lancet.* 2005;366(9497):1653–1666

Clinical Features, Pathogenesis, and Treatment of Guillain-Barré Syndrome. van Doorn PA, Ruts L, Jacobs BC. *Lancet Neurol.* 2008;7(10):939–950 lymphocytic predominance. Electromyography results may show conduction abnormalities depending on the GBS subtype. Last, MRI findings, although nonspecific, may show gadolinium enhancement of the spinal nerve roots.

For initial management, patients require close monitoring of motor, autonomic, and respiratory function in the inpatient setting. Immunotherapy with intravenous immunoglobulin (IVIG) or plasma exchange is the preferred treatment modality but should be reserved for patients with severe GBS. Severe symptoms include progressive muscle weakness, respiratory compromise, bulbar symptom development, or the inability to walk unassisted. Although there are no clear inferiority or superiority outcome trials, IVIG is typically selected over plasma exchange due to ease of administration and greater availability. The total dose of IVIG in children is 2 g/kg, given as 1 g/kg for 2 days or 400 mg/kg for 5 days, usually as a single treatment course. The proposed mechanism of action of IVIG is suppression of the inflammatory and immune-mediated responses. In patients with mild disease or nonprogressive symptoms, treatment may be supportive. Once stabilized, physical, occupational, and speech therapies should be initiated early to restore and maintain function. Mortality is estimated to be 3% to 4%. Children typically have a better prognosis than adults, and in previous studies, greater than 80% of children had excellent long-term recovery regardless of subtype. The recurrence risk is estimated to be 2% to 5%.

COMMENTS: Although it is fortunate that children tend to experience less severe disease than adults, I am struck by the variability of presentations. Although usually a monophasic disease, in some patients it may reoccur, with a mean interval to reoccurrence of 7 years. Early and timely diagnosis is important because studies have suggested improved outcomes when treatment is initiated within the first 2 weeks. Although in most patients the maximal weakness presents in the first 2 weeks, in some it may take up to 4 weeks, so it is important to have GBS in your differential diagnosis. The elevated protein level in the CSF may not initially be present but is present in approximately 50% of patients in the first week and in greater than 90% of patients after the second week of symptoms. Up to 20% of patients (when including adults) remain with some disability. Although much progress has been made, more research is needed. Active areas of research include assessing treatment effectiveness in patients with more mild disease and the best strategies to treat autonomic dysfunction and related fatigue noted in patients with GBS.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

- Chapter 260: Guillain-Barré Syndrome - https://pediatriccare.solutions.aap.org/chapter.aspx?sectionId=135886435&bookId=1626

Point-of-Care Quick Reference

- Guillain-Barre Syndrome - https://pediatriccare.solutions.aap.org/content.aspx?gbosid=311264

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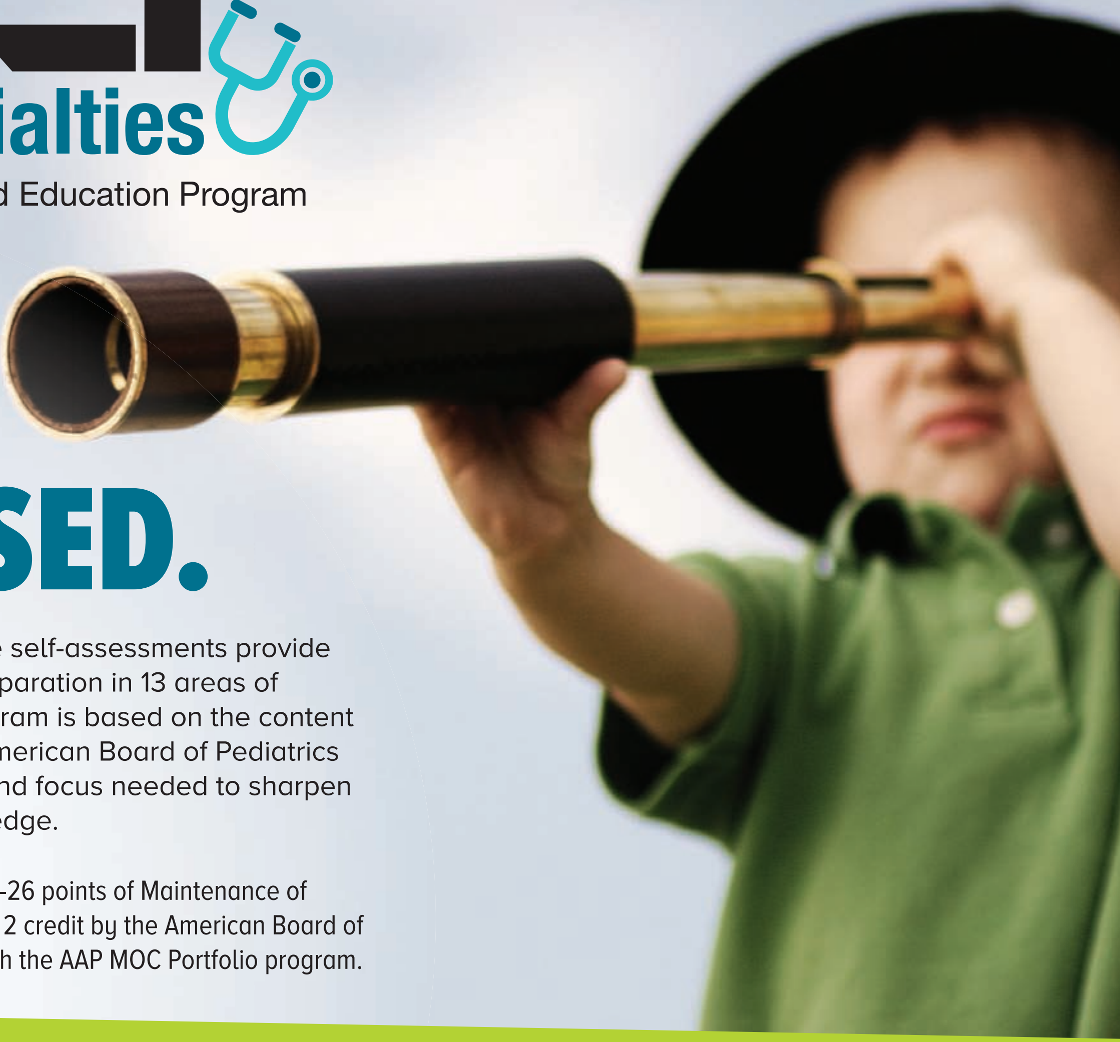
Correction

An omission on screening guidelines appeared in the December 2017 review “Postpartum Depression: What Do Pediatricians Need to Know?” (Sriraman NK, Pham D, Kumar, R. *Pediatrics in Review*. 2017;38(12):541–551). According to current recommendations, screening for postpartum depression should take place at the 1-, 2-, 4-, and 6-month well-child visits. The online article has been updated to reflect this recommendation, and a correction was published online. The journal regrets the error.



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Visual Diagnosis

A Toddler with a Large Birthmark and Developmental Delay

Amarilis A. C. Martin, MD,* Muhammad Ubaidulhaq, MD,† Lalitha Sivaswamy, MD*†

**Department of Pediatrics and †Department of Pediatric Neurology, Children's Hospital of Michigan, Detroit Medical Center, Detroit, MI*

PRESENTATION

A 17-month-old girl with a normal perinatal history presents to the clinic with chief complaints of a large skin lesion and developmental delay.

The toddler was born to nonconsanguinous healthy parents at a birthweight of 3,900 g. She developed hydrocephalus at age 3 months for which she received a ventriculoperitoneal shunt. At 9 months of age she was noted to be markedly delayed in all aspects of development, and 1 month later she was diagnosed as having conductive hearing loss. A subsequent sleep study, performed for stridor at night, demonstrated obstructive sleep apnea secondary to laryngomalacia, for which a supraglottotomy procedure was performed. She developed scoliosis and hip dysplasia at approximately 1 year of age (Fig 1); the latter was treated with left adductor and psoas tendonotomy.

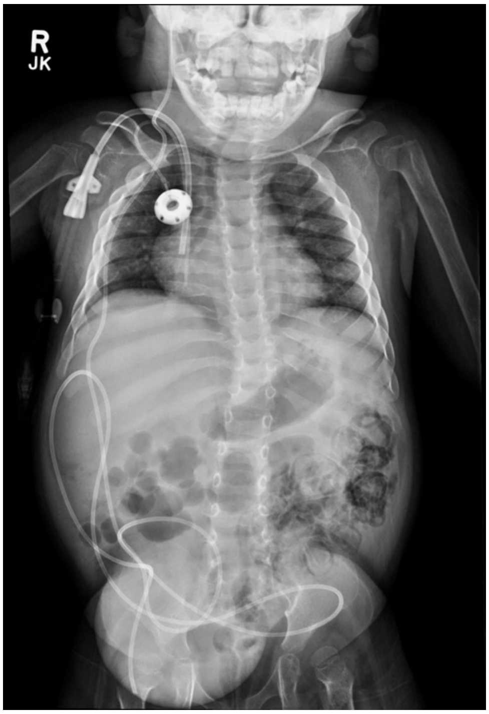

Figure 1. Spine radiograph. Upright frontal view shows a ventroperitoneal shunt catheter. There is mild levoconvex curvature of the thoracolumbar spine, with the apex at the T10-T11 level and dislocation of the left femoral head.

AUTHOR DISCLOSURE Drs Martin, Ubaidulhaq, and Sivaswamy have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

At presentation, the physical examination reveals an alert and interactive toddler with a head circumference of 20.1 in (51.0 cm) (>99th percentile), mild coarsening of facial features, an extensive dermal melanocytosis covering most of her back, macroglossia, a prominent umbilical hernia, and hepatomegaly (Figs 2 and 3). Developmentally, she can roll from her back to her stomach but cannot sit independently. She has 5 discernable words and follows no instructions. She has moderate hypotonia of her extremities, normal deep tendon reflexes, and downward plantar responses. Her constellation of signs and symptoms raises concern for an inborn error of metabolism.

DIAGNOSIS

Magnetic resonance imaging (MRI) of the brain demonstrates a thin corpus callosum and multiple dilated Virchow-Robin spaces surrounding the vessels as they travel from the subarachnoid space through the brain parenchyma, in the periventricular white matter (Fig 4). On further testing, her urine shows elevated levels of the glycosaminoglycans dermatan sulfate, heparan sulfate, and chondroitin sulfate. Two distinct heterozygous mutations for the lysosomal enzyme alpha-L-iduronidase (IDUA) are found, establishing a diagnosis of Hurler syndrome.

DISCUSSION

Hurler syndrome is one of the most severe forms of the mucopolysaccharidoses (MPSs), a group of lysosomal storage disorders caused by a deficiency in the activity of a lysosomal enzyme. In Hurler syndrome, deficiency of lysosomal enzyme IDUA leads to progressive accumulation of glycosaminoglycans and other compounds catabolized in the lysosome. The accumulated molecules subsequently "spill over" from the lysosome into the cell and eventually from the cell into adjacent tissues, the cerebrospinal fluid, and

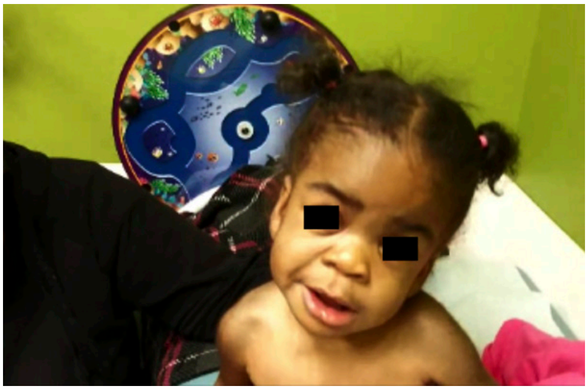

Figure 2. Macrocephaly, course facial features, flattened nasal bridge, and torticollis with poor head control are demonstrated at 17 months of age.

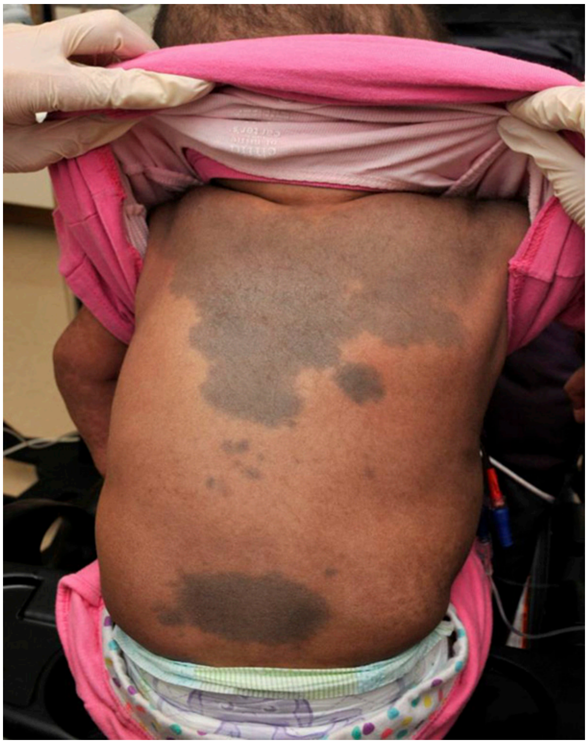

Figure 3. Large, confluent, bluish skin lesion is demonstrated on the back of the child.

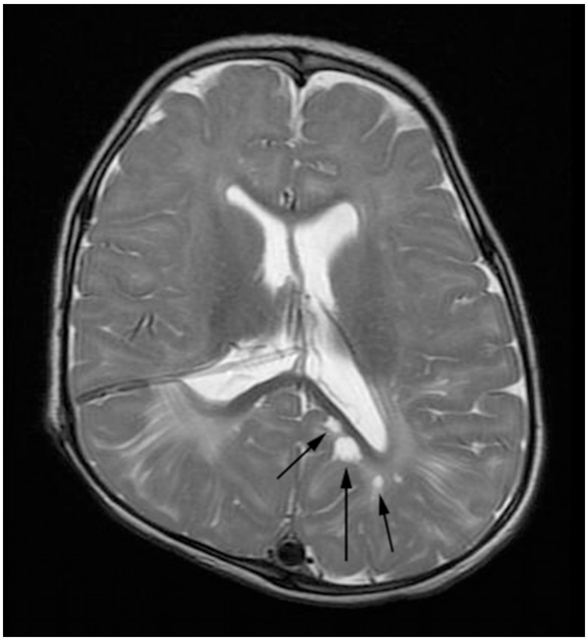

Figure 4. Brain axial T2 magnetic resonance image shows a shunt catheter exiting from the posterior horn of the right lateral ventricle. Multiple cerebrospinal fluid intensity cystic areas are noted in the retrotrigonal white matter (arrows).

the systemic circulation. In addition to causing organomegaly, the accumulation of these molecules in tissues prevents further glycosaminoglycan activity and alters multiple intracellular pathways. Patients with MPS have defective cellular growth and development, increased oxidative stress, abnormal cellular Ca^{2+} and H^{+} homeostasis, cell apoptosis, abnormal trafficking of other molecules catabolized in the lysosome, and neurosynaptic dysfunction. (1) An inflammatory response results with progressive increase of storage burden.

Although each type of MPS is rare, the overall incidence is not negligible (1 of 25,000 live births), with Hurler syndrome being the most common type. (2) Hurler syndrome is autosomal recessive, affecting males and females equally. (3)

Clinical Features

Patients with Hurler syndrome may be asymptomatic and seemingly normal in the first several weeks or months after birth. However, signs of neurologic and somatic damage appear within the first year after birth with rapid progression, leading to disability within 12 to 18 months after onset and death before the 10th birthday if untreated. (3)(4) Patients have extensive cognitive impairment, progressive and inexorable regression, and behavior changes. Conductive and sensorineural hearing loss, teeth and gum abnormalities, and macroglossia contribute to speech delay. (5) Common brain MRI findings include diffuse white matter lesions in the periventricular region and subcortical regions of the parietal and occipital lobes, "honeycomb-like" lesions in basal ganglia and thalami, brain atrophy, ventriculomegaly (due to communicating hydrocephalus), and variable-sized arachnoid cysts filled with cerebrospinal fluid in the anterior cranial fossa. (2) Impaired vision may be due to optic nerve swelling, corneal clouding, or glaucoma. Children with MPS are at high risk for multiple disorders of the upper airway and ears, including rhinitis, recurrent otitis media, upper airway obstruction leading to obstructive sleep apnea, and tracheomalacia. These children are also at high risk for recurrent lower respiratory infections and acute respiratory failure. Heart murmurs may signify myocardial hypertrophy, systolic dysfunction, or cardiac valve abnormalities. Abdominal distention, hepatosplenomegaly, and inguinal or umbilical hernias are common. Feeding problems, chronic diarrhea, and kidney involvement may be present. (6)(7) Hurler syndrome is the most common lyososomal storage disorder associated with dermal melanocytosis, which is usually generalized and involves the dorsal and ventral trunk in addition to the extremities and sacral area. (8)

Children affected by MPS develop defective ossification (dysostosis multiplex) and characteristically develop multiple bony anomalies, such as coarse facies (frontal bossing, prominent eyes, hypertelorism, depressed nasal bridge, gapped teeth, gingival hypertrophy), odontoid hypoplasia (which predisposes to atlanto-axial subluxation and subsequent spinal cord compression), skeletal deformities (such as gibbus and scoliosis), carpal tunnel syndrome, multiple joint contractions, and claw hand deformity. These patients are predisposed to motor disability and short stature. (3)(4)(5)(6)

Diagnostic Tests

High or abnormal patterns of urinary glycosaminoglycan levels (quantitative) are suggestive of MPS, and the presence of a specific glycosaminoglycan (qualitative) in the urine can suggest an MPS subtype. The diagnosis is confirmed by IDUA enzyme activity measurements (gold standard) using fibroblasts or leukocytes (skin or punch biopsy), serum (dried blood spots), chorionic villi cells, or amniocytes. Gene sequencing may follow biochemical diagnosis to identify the specific mutation(s) and to evaluate at-risk family members. Radiography and MRI may be helpful in suggesting and supporting MPS as a possible diagnosis, for monitoring the course of the disease, for surgical and medical planning, and for assessing the impact of therapy. (2)(3)(5)(6)(7)

Differential Diagnosis

The differential diagnosis of Hurler syndrome is vast and can include hydrocephalus, rickets, hypothyroidism, chondrodystrophy, epiphyseal or metaphysical dysplasia, osteogenesis imperfecta, or spondyloepiphyseal dysplasia. Taking the conglomeration of signs seen in Hurler syndrome, multiple sulfatase deficiency and mucolipidosis types I to IV should be ruled out. (7)

Management

In addition to providing symptomatic and supportive care by a multidisciplinary team, 2 treatment options exist: hematopoietic stem cell transplant (HSCT) and enzyme replacement therapy (ERT) for those who are poor candidates for HSCT. Gene therapy is in clinical trials. (4)

Children with Hurler syndrome who are younger than 2 years of age with a developmental quotient of at least 70% of normal are ideal candidates to receive HSCT from bone marrow or umbilical cord. (5) Hematopoietic stem cell transplant has improved survival significantly, with some children surviving beyond their 20th birthday. (4) Also, HSCT leads to improved or preserved neurocognition and reduced somatic abnormalities, although the progression of musculoskeletal disease, vision, and cardiac valve disease may not be arrested despite HSCT. Hematopoietic stem cell transplant still carries significant risk of morbidity and mortality; however, if ERT is started 6 weeks before HSCT and is continued until engraftment is established, there is improved survival and a lower incidence of graft-versus-host disease. (3)(4)(6)

Enzyme replacement therapy with intravenous infusions of recombinant IDUA (ie, laronidase) stabilizes or improves some somatic aberrations, decreases urinary glysoaminoglycan levels, and improves quality of life. (9) Unfortunately, laronidase is too large of a protein to cross the blood-brain barrier, and greater than 90% of patients develop 1 or more infusion-associated reactions, such as headache, flushing, fever, rash, and sometimes life-threatening anaphylaxis. (4)(10) Although infusion-associated reactions decrease with time, they can be prevented with antipyretic and/or antihistamine pretreatments. Methods to get exogenous enzyme to the brain are under investigation. (4)

Patient Course

By 12 months of age, the patient already had developed hydrocephalus, developmental delay, hearing loss, airway obstruction, and skeletal abnormalities, which were clues to her diagnosis. Earlier recognition of dysostosis multiplex, corneal clouding, and her coarse facial features would have helped establish the diagnosis sooner. As the case demonstrates, early diagnosis of Hurler syndrome remains a challenge for multiple practitioners. Nevertheless, it is imperative to diagnose and treat the condition before irreversible changes occur, ideally before 2 years of age.

The patient received weekly laronidase infusions until she underwent successful HSCT. Her hepatomegaly resolved, her head circumference decreased, and her global development showed some improvement. Despite appropriate therapy, however, she developed graft-versus-host disease that flared on discontinuation of a post-HSCT corticosteroid course; she died of lung and gastrointestinal involvement at age 33 months, 10 months after HSCT.

Summary

- Hurler syndrome is a multisystem, progressive, irreversible disease.
- It is imperative that patients have regular follow-up with the pediatrician, neurologist, hematologist, orthopedic surgeon, and ophthalmologist.
- Family counseling, individual counseling, and support groups such as the National MPS Society may help patients and their families cope with the challenges that arise with this syndrome. (4)

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The Many Faces of Guillain-Barré Syndrome

Most of us learned the basic clinical manifestations of Guillain-Barré syndrome in medical school and likely have encountered at least a few children with the condition during residency or in practice. Four January 2018 *Pediatrics in Review* articles focus on this immune-mediated peripheral neuropathy, emphasizing some of its less common clinical patterns that are apt to be less familiar to most physicians.

In their *In Brief* on the topic, Chung and Deimling (1) summarize the classic manifestations of Guillain-Barré syndrome. This is an acute-onset, immune-mediated peripheral neuropathy that likely is triggered by an infection or another immune stimulus. Guillain-Barré syndrome classically presents as an acute-onset, rapidly progressive, flaccid weakness starting in the legs, associated with diminished or absent tendon reflexes. The clinical severity of Guillain-Barré syndrome varies, but at its worst, it can lead to respiratory insufficiency and death. The cerebrospinal fluid (CSF) typically exhibits an elevated protein level but not an excess of white blood cells, although this pattern is not always present initially, and occasionally individuals have a mildly elevated white blood cell count. (1)

In *Index of Suspicion Case 3,* Bassal and Lupo (2) present an 11-year-old boy with a 2-day history of gait unsteadiness and diplopia. His examination revealed initially diminished then absent tendon reflexes, dysmetria, and partial dysfunction of cranial nerves III and VI. His extremity muscles were not weak. Results of imaging and laboratory investigations were normal except for elevation of antiganglioside anti-GQ1b immunoglobulin G antibodies.

The differential diagnosis of acute ataxia is extensive. (3) This boy's diagnosis is Miller Fisher syndrome. Generally considered to be a milder variant of Guillain-Barré syndrome, Miller Fisher syndrome features a triad of areflexia, ataxia, and cranial neuropathy. (4) Most individuals with Miller Fisher syndrome recover completely, with or without therapy. Nonetheless, prompt recognition of Miller Fisher syndrome may prevent unnecessary diagnostic tests, and occasionally patients progress to the riskier Guillain-Barré syndrome.

In *Index of Suspicion Case 1,* Shah et al (5) describe a 5-year-old boy with right leg pain and difficulty walking for 5 days. His right leg was weak and tender to palpation. Tendon reflexes were absent in the right leg. Left leg strength was normal, but even on the left his reflexes were diminished. This presentation might suggest a localized joint problem, but hip magnetic resonance imaging (MRI) findings were normal. Weakness in 1 limb would once have suggested poliomyelitis, which often presents in this manner. More recently, asymmetrical flaccid paralysis due to acute myelitis has been described. (6)

This boy too proved to have a variant of Guillain-Barré syndrome. His CSF revealed increased protein and immunoglobulin G levels. An MRI of the thoracic and lumbar spine documented asymmetrical contrast enhancement of ventral and dorsal nerve roots, and a nerve conduction velocity test confirmed axonal

AUTHOR DISCLOSURE Dr Roach has disclosed that he receives an honorarium from Elsevier for serving as editor of *Pediatric Neurology*. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

polyneuropathy in both legs. Back or leg pain is common in children with Guillain-Barré syndrome. The weakness of Guillain-Barré syndrome is typically symmetrical, but as this child illustrates, it isn't always.

In *Index of Suspicion Case 2,* Bashir and Aarons (7) describe a 2-year-old girl who refused to walk for 3 weeks. Based on the tests and treatments initially recommended, her symptoms at first were attributed to musculoskeletal disease. When examined, she had no tendon reflexes in the legs and could not dorsiflex the right foot. Movement of her legs seemed to elicit pain. Eventually an MRI demonstrated abnormal spinal nerve roots, and a lumbar puncture confirmed an elevated CSF protein level in the absence of inflammatory cells.

Persistent, painful dysfunction without complete paralysis has a broad differential diagnosis that includes several conditions that are far more common than Guillain-Barré syndrome. The symptoms of toxic synovitis usually improve with the use of nonsteroidal anti-inflammatory agents and heat. Septic arthritis, diskitis, and osteomyelitis were eliminated because of her lack of fever and normal laboratory test results. Postinfectious myositis could have explained her signs and symptoms. A spinal cord lesion, such as a tumor or epidural empyema, must be considered in this setting.

It is important to recognize not only classic Guillain-Barré syndrome but also its less obvious patterns. (8) Children often improve spontaneously or in response to intravenous immunoglobulin therapy or plasmapheresis, and as is often the case, earlier treatment is generally more effective. There are potentially life-threatening complications of Guillain-Barré syndrome, including respiratory failure and autonomic dysfunction with systemic hypertension or cardiac arrhythmias. These 4 recent articles together provide an excellent overview of both the classic and the atypical manifestations of the syndrome.

E. Steve Roach, MD

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Pediatric Solid Tumors of Infancy: An Overview

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Practice Gaps

Pediatricians should recognize the role of age, genetic factors, and syndromes that predispose to the development of certain pediatric solid tumors. Many symptoms of common childhood illnesses that progress or do not resolve in a timely manner should require a detailed evaluation and prompt referral to a cancer specialist.

Objectives

After completing this article, readers should be able to:

1. Recognize the presenting signs and symptoms of pediatric solid tumors (eg, abdominal mass, constipation, shortness of breath, back pain, bone pain, fever, and hypertension).
2. Identify the signs and symptoms of retinoblastoma, neuroblastoma, hepatoblastoma, and Wilms tumor.
3. Recommend genetic evaluation and close disease surveillance for patients with certain solid tumors or particular predisposing conditions.
4. Recognize general aspects of the multidisciplinary treatment approach in children with retinoblastoma, neuroblastoma, hepatoblastoma, and Wilms tumor.

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ABBREVIATIONS

AFP	α-fetoprotein
ASCT	autologous stem cell transplant
CT	computed tomography
FDA	Food and Drug Administration
MRI	magnetic resonance imaging
OMS	opsoclonus myoclonus syndrome
VIP	vasoactive intestinal peptide
^{123}I-MIBG	^{123}I-meta-iodo-benzylguanidine

INTRODUCTION

Pediatric solid tumors are a group of nonhematologic, extracranial cancers that occur during childhood. This heterogeneous group of tumors represents approximately 40% of all pediatric cancers (Fig 1). Many pediatric solid tumors are referred to as embryonal or developmental cancers because they arise in young children or adolescents as a result of alterations in the processes of organogenesis or normal growth. In this review, we address common symptoms developed in children diagnosed as having malignant solid tumors and offer a general description of the most common pediatric solid tumors in infants and young children. Common malignant solid tumors in adolescents will be addressed in a separate article.

PRESENTING SYMPTOMS OF PEDIATRIC SOLID TUMORS

The rarity of solid tumors combined with a variety of symptoms observed across different tumor types renders timely diagnosis of these conditions difficult.

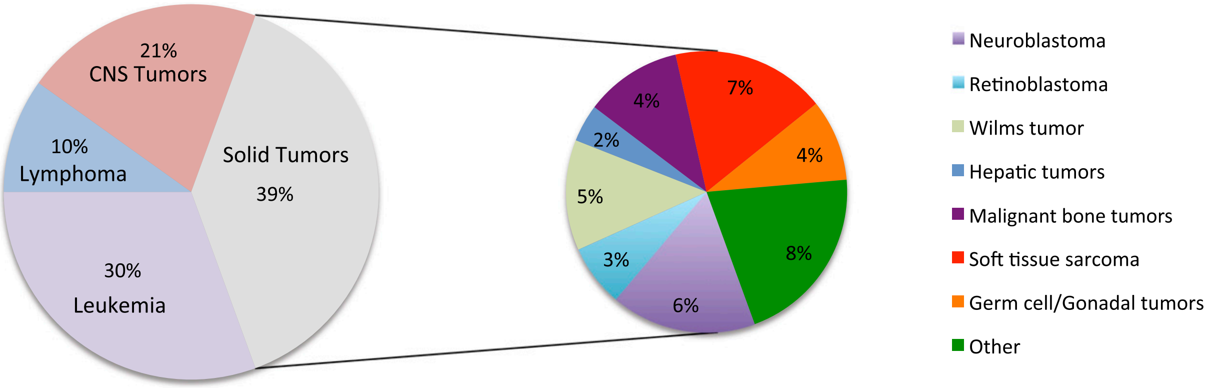

Figure 1. Percentage distribution of pediatric cancers and solid tumors in children (0–14 years old).

Many presenting signs and symptoms of pediatric solid tumors mimic those of common childhood illnesses, which makes it critically important for primary care providers to consider malignancy in their differential diagnoses and to understand indications for further diagnostic evaluation to rule out a solid malignancy in a child or adolescent. The age of the patient can be helpful in the differential diagnosis of any mass identified on physical examination (Table).

Abdominal Masses

One of the most common presenting signs of solid tumors in children is a palpable abdominal mass. Often, the mass is brought to the attention of the primary care provider by a parent or guardian. Although there are a variety of benign abdominal masses, all abdominal masses require further diagnostic evaluation. Most malignant abdominal masses are found in children ages 1 to 5 years, with Wilms tumor and neuroblastoma being the most common. Children with Wilms tumor often appear well aside from the palpable mass but may have urinary symptoms such as hematuria, frequency, or incontinence. Children with neuroblastoma are more likely to have associated symptoms such as fatigue, fever, pain, or weight loss. Plain abdominal radiography and abdominal ultrasonography are good initial diagnostic steps for a child with an abdominal mass. More complex tests, such as computed tomography (CT) or magnetic resonance imaging (MRI), should be performed at a tertiary center with sufficient experience in diagnostic imaging of pediatric tumors.

TABLE. **Tumor Location and Differential Diagnosis of Common Malignant Solid Tumors in Pediatric Patients**

TUMOR	NEWBORN (<1 Y)	INFANT (1–3 Y)	CHILD (3–11 Y)	ADOLESCENT/YOUNG ADULT (12–21 Y)
Abdominal	Neuroblastoma Mesoblastic nephroma Hepatoblastoma Wilms tumor	Neuroblastoma Wilms tumor Hepatoblastoma Rhabdomyosarcoma	Neuroblastoma Wilms tumor Rhabdomyosarcoma	Germ cell tumor Soft tissue sarcoma Hepatocellular carcinoma
Extremity	Fibrosarcoma	Fibrosarcoma Rhabdomyosarcoma Ewing sarcoma	Rhabdomyosarcoma Ewing sarcoma	Osteosarcoma Ewing sarcoma Soft tissue sarcoma
Genitourinary	Teratoma	Rhabdomyosarcoma Yolk sac tumor Clear cell sarcoma of the kidney	Rhabdomyosarcoma	Germ cell tumor Teratoma
Head and neck	Retinoblastoma Neuroblastoma Rhabdomyosarcoma	Retinoblastoma Neuroblastoma Rhabdomyosarcoma	Rhabdomyosarcoma	Soft tissue sarcoma Nasopharyngeal carcinoma
Thoracic	Neuroblastoma Teratoma	Neuroblastoma Rhabdomyosarcoma Teratoma	Neuroblastoma	Ewing sarcoma

Thoracic Masses

Similar to abdominal masses, all masses that arise in the thorax require further diagnostic evaluation. Patients with mediastinal masses often present with signs of compression of surrounding structures, including the airway or vasculature, but the mass may present as an incidental finding on a chest radiograph obtained for unrelated reasons. Compression of the airway frequently causes respiratory symptoms such as dyspnea, wheezing, or persistent nonproductive cough not relieved by β-agonist treatment. Vascular compression can result in superior vena cava syndrome, which manifests as facial edema. Masses in the anterior, middle, or posterior mediastinum all may represent malignancy. Anterior mediastinal masses that cause respiratory and vascular compromise frequently are teratomas and most commonly are diagnosed in older adolescents. Masses found in the middle mediastinum are likely to be lymphoma; however, sometimes abdominal solid tumors such as neuroblastoma and rhabdomyosarcoma can metastasize to middle mediastinal lymph nodes. Posterior mediastinal masses generally are neurogenic tumors such as neuroblastoma and ganglioneuroblastoma. Patients with these posterior mediastinal masses may present with signs and symptoms of spinal cord compression, including back pain, paresthesia, weakness, or paralysis. Persistent back pain is unusual in children and should trigger a detailed history and physical examination. Respiratory, vascular, and spinal cord compressions are oncologic emergencies. Patients should be sent to the emergency department for immediate evaluation. Special precautions should be taken into consideration when performing diagnostic imaging studies or other procedures under sedation if airway compression is suspected because supine positioning and muscle relaxation from sedation can exacerbate an already narrowed airway, leading to rapid and sometimes irreversible respiratory failure.

Fever

Although malignancy is part of the differential diagnosis of fever of unknown origin, it is unlikely to be the sole presenting symptom of a patient with a solid tumor. Solid tumors that manifest with systemic symptoms such as fever include neuroblastoma and Ewing sarcoma. Neuroblastoma will often have accompanying symptoms such as a palpable abdominal mass, generalized malaise, or other unusual but specific symptoms, such as hypertension, Horner syndrome, or opsoclonus-myoclonus-ataxia. Ewing sarcoma often is accompanied by a palpable mass, pain, or limping.

Bone Pain

Pain is a common presenting symptom for patients diagnosed as having childhood cancer. Bone pain that is localized and progresses in severity should serve as a warning sign for the pediatrician and not be dismissed. In addition, limping or refusal to bear weight is another common sign for children diagnosed as having cancer. Diffuse bone pain can be a manifestation of metastatic solid tumors or hematologic malignancies such as leukemia. Bone pain that is accompanied by systemic symptoms such as night sweats, weight loss, or fever should raise the suspicion of an underlying malignancy. Plain radiographs of the affected area should be obtained in patients with bone pain when cancer is suspected. The presence on plain films of an osteolytic or osteoblastic lesion with or without classic radiologic signs of malignancy, such Codman triangle, sunburst pattern, or onion skin appearance, requires prompt referral to a pediatric oncologist or an orthopedic oncologist. The most common primary bone tumors are osteosarcoma and Ewing sarcoma, which are seen mainly in adolescents and young adults.

COMMON PEDIATRIC SOLID TUMORS IN YOUNG CHILDREN

Most pediatric solid tumors are thought to arise from aberrant tissue formation during the normal process of organ development in early infancy or rapid growth in puberty. This article focuses on the clinical manifestations of retinoblastoma, neuroblastoma, hepatoblastoma, and Wilms tumor, the most common pediatric solid tumors in infancy and early childhood.

Retinoblastoma

Retinoblastoma is a malignant tumor that arises from the developing retina in very young children. There are approximately 280 new cases of retinoblastoma diagnosed each year in the United States. The incidence of retinoblastoma is not equally distributed around the world. It seems to be higher in Southeast Asia and South America. The reason for this difference is unknown, although it is thought to be related to genetic and socioeconomic factors. The incidence of retinoblastoma is similar in boys and girls. Approximately 75% of patients with retinoblastoma are diagnosed before reaching age 2 years. Patients with bilateral disease present at an even younger age, usually around 12 months of age. Retinoblastoma can occur as a heritable (25% of cases) or nonheritable (75%) disease. Germ-line mutation in the *RB1* gene, found on the long arm of chromosome 13, characterizes patients with heritable retinoblastoma. These patients usually present with bilateral disease and develop retinoblastoma at a younger age. Individuals who carry the *RB1* mutation also have increased risk of developing other cancers, such as osteosarcoma, soft tissue sarcomas, or melanoma. Therefore, primary care providers should ensure that families and patients diagnosed as having retinoblastoma seek genetic counseling and molecular testing. The information obtained from additional genetic testing can help estimate the risk of developing other cancers or the need for close surveillance in patients and their siblings.

Presentation and Diagnosis. The role of primary care providers is essential in the prompt recognition of leukocoria, white pupillary reflex (Fig 2) instead of the normal red reflex, or strabismus as common manifestations of this malignancy. The American Academy of Pediatrics policy statement recommends evaluation of red reflex periodically as part of regular health supervision visits for the first 5 years after birth. Any asymmetry in the color of the retina or the presence of white spots on physical examination, as well as information provided by the parents regarding asymmetric pupils noted in photographs of the child, should prompt a dilated eye examination under sedation by an ophthalmologist. The early diagnosis of retinoblastoma may be a key factor to prevent extraocular spread, salvage the ocular globe, and preserve vision.

The diagnosis of intraocular disease, retinoblastoma localized to the eye, usually does not require tumor histologic confirmation; therefore, tumor biopsy should not be attempted. Diagnosis and medical treatment are based on direct visualization of retinoblastoma on comprehensive ophthalmologic examination under anesthesia. If enucleation (removal of the ocular globe) is required, evaluation of the enucleated eye should be made by an experienced pathologist to determine the presence of high-risk features, such as choroid involvement or tumor beyond the lamina cribosa, which would require adjuvant therapies. These high-risk features increase the likelihood of extraocular retinoblastoma, with disease extending to the orbit, central nervous system, and, rarely, bone marrow or lymph nodes. Most patients require an MRI of the brain and orbits for complete tumor-staging evaluation. Bone marrow aspirates, bone scintigraphy, and lumbar puncture are usually not indicated unless there is suspicion for systemic spread.

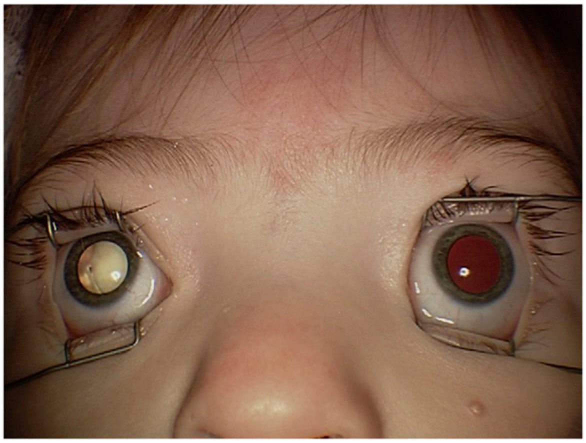

Figure 2. Photograph of leukocoria on the right eye of a patient with retinoblastoma. Red reflex is present on the left eye. (Photo courtesy of Dan S. Gombos, MD, FACS.)

Risk Grouping and Treatment. The treatment of retinoblastoma requires a multidisciplinary team approach in specialized centers. Treatment options are dictated by the extent of intraocular, extraocular, and distant metastatic disease and have 3 main goals: to save the patient's life, to preserve vision, and to avoid late-treatment sequelae. Although enucleation generally provides definitive management of the affected eye, in many cases, both vision and the eye can be salvaged using locally directed therapies with or without systemic chemotherapy. In more advanced ocular disease, enucleation may be indicated. In the most advanced cases, high-dose chemotherapy with autologous stem cell transplant (ASCT) and radiotherapy may be necessary. When detected in the early stages, retinoblastoma is a highly curable disease, with more than 90% of patients with localized intraocular disease achieving a long-term cure. However, patients with extraocular or metastatic disease have overall survival of only 50% to 80%, highlighting the importance of early detection. Children with central nervous system involvement particularly have a very poor prognosis. Unfortunately, patients with retinoblastoma in resource-limited countries often reach medical attention with advanced disease, and outcomes in these countries remain lower than those in high-income countries.

Although the outcomes for retinoblastoma are excellent, survivors of retinoblastoma are at high risk for developing second malignant neoplasms. Patients previously treated with radiotherapy are at high risk for sarcomas inside and outside of the radiation field. In addition, those with heritable retinoblastoma have a markedly increased risk of developing a second neoplasm, including some epithelial cancers, sarcomas, and melanoma, independently of radiotherapy.

Neuroblastoma

Neuroblastoma, the most common extracranial tumor in children, accounts for 8% of all pediatric cancers. An estimated 700 new cases are diagnosed each year in the United States. The incidence of neuroblastoma is slightly higher in boys than in girls, and the disease affects more white children than those of other races/ethnicities in the United States. The incidence of neuroblastoma is fairly uniform in industrialized nations and seems to be lower in Sub-Saharan Africa for reasons that are unknown. The median age at diagnosis is 19 months, with most patients diagnosed between 0 and 5 years of age. Most cases of neuroblastoma occur in children with no family history or an associated condition. Less than 2% of cases occur in patients with a positive family history, and these patients tend to be diagnosed earlier and may have more than 1 primary tumor. Mutations in the *ALK* gene are found in 75% to 80% of cases of familial neuroblastoma and in 10% of sporadic cases. Mutations in the *PHOX2B* gene are also responsible for approximately 5% of hereditary neuroblastomas and are associated with other neural crest disorders, including Hirschsprung disease and central hypoventilation.

Presentation and Diagnosis. Neuroblastoma has a varied clinical presentation. Tumors may arise from the adrenal glands or anywhere along the sympathetic chain. Presentation of disease varies from asymptomatic tumors detected incidentally to systemic life-threatening illness, depending on the extent and location of the disease. Approximately half of all patients have localized or locoregional disease at diagnosis. Abdominal masses account for 75% of primary tumors and present with fullness, constipation, abdominal pain, distention, or hypertension from compression of renal vessels. Thoracic and cervical tumors may be asymptomatic, cause respiratory symptoms from airway compression, or present with Horner syndrome or, rarely, superior vena cava syndrome. Paraspinal tumors may extend into the spinal column and lead to spinal cord compression with resultant weakness, loss of deep tendon reflexes, bowel and bladder dysfunction, and paralysis sometimes resulting in paraplegia. Approximately half of all patients will present with metastatic disease at diagnosis, and these patients may have systemic symptoms, including fever, weight loss, cachexia, and bone pain leading to limping and irritability. The most common sites for metastatic disease include bones, bone marrow, and liver. Neuroblastoma also frequently spreads to the skull and orbital bones, leading to a classic presentation characterized by periorbital ecchymosis, referred to as "raccoon eyes."

Two paraneoplastic syndromes are associated with neuroblastoma. Opsoclonus myoclonus syndrome (OMS) is seen in 2% to 3% of patients with neuroblastoma and manifests with myoclonus, ataxia, and opsoclonus, a rapid chaotic eye movement. Although most patients with this syndrome have low-stage and low-risk neuroblastoma, their neurologic outcomes are, unfortunately, not as favorable. As many as 80% of these children will have long-term cognitive and motor delays, language deficits, and behavioral problems. Resection of the neuroblastoma may improve symptoms temporarily, but many patients experience recurrence or persistence of OMS. The second paraneoplastic syndrome, vasoactive intestinal peptide (VIP) syndrome, is caused by neuroblastoma tumors secreting VIP. This syndrome presents as abdominal distention, intractable watery diarrhea, hypokalemia, and dehydration. Unlike OMS, resecting the tumor generally cures this condition because VIP is secreted directly by the tumor. Young infants with neuroblastoma may have a distinctive disease presentation with massive hepatomegaly as a result of tumor infiltration of the liver that may result in respiratory compromise from an enlarged abdomen. In addition, young infants may present with skin involvement, characterized by bluish subcutaneous nodules. The role of primary care providers is to recognize the myriad of symptoms with which patients with neuroblastoma may present and to initiate their evaluation and prompt referral.

Most commonly, neuroblastoma is diagnosed on tumor histopathologic analysis of a biopsy specimen. The diagnosis may also be made by finding an elevation in urine or serum catecholamine levels and detecting tumor cells in bone marrow. Staging evaluation includes tumor imaging with CT or MRI. Generally, cross-sectional imaging of the chest, abdomen, and pelvis are performed in the initial evaluation. Distant metastatic disease is evaluated using ^{123}I-meta-iodo-benzylguanidine (^{123}I-MIBG) scintigraphy; ^{123}I-MIBG is a radiolabeled chemical analogue of norepinephrine that is selectively concentrated in sympathetic nervous tissues, such as neuroblastoma, and is sensitive and specific for neuroblastoma. If the primary tumor is not seen with ^{123}I-MIBG scintigraphy, positron emission tomography or bone scanning can be used to detect metastatic disease. To evaluate for bone marrow metastasis, bone marrow aspirate and biopsy from at least 2 sites (generally bilateral iliac crests) are performed. Brain imaging is required when clinically indicated based on symptoms or to evaluate the extent of cranial lesions on ^{123}I-MIBG scintigraphy.

Risk Grouping and Treatment. Patients with neuroblastoma are divided into 3 risk groups—low, intermediate, and high—based on risk of disease recurrence. The risk groups are defined based on a variety of clinical and biological factors, and treatment has been tailored to address the specific prognosis of each group. Patients with higher-stage tumors, particularly metastatic tumors, and patients older than 18 months at diagnosis have worse outcomes. Many biological risk factors, including tumor histologic appearance, DNA ploidy, certain chromosomal deletions or gains, and, importantly, amplification of the oncogene *MYCN,* are included in risk stratification.

Patients with low- and intermediate-risk neuroblastoma represent a heterogeneous group with excellent outcomes. Low-stage tumors with favorable biological markers often do not metastasize, and, therefore, surgical resection may be curative. Chemotherapy is reserved for patients with life- or organ-threatening symptoms, such as spinal cord compression or respiratory compromise. Treatment for intermediate-risk neuroblastoma comprises moderate doses of multi-agent chemotherapy and surgical resection. Neuroblastoma in infants (<1 year of age) tends to regress without treatment. In addition, children younger than 18 months with metastatic neuroblastoma limited to the skin, liver, and bone marrow also may demonstrate spontaneous regression, allowing for observation. However, a subset of infants does require immediate treatment owing to their high risk for complications and death from massive hepatomegaly, liver dysfunction, and respiratory distress.

High-risk neuroblastoma is an aggressive disease with an overall poor outcome. Long-term survival remains less than 50% in large cooperative group studies regardless of more intense and prolonged therapy. High-risk neuroblastoma therapy comprises 3 phases: induction chemotherapy, consolidation, and maintenance therapy. Induction chemotherapy includes high-intensity, multidrug chemotherapy and local-control surgical resection with the goal of maximally reducing tumor bulk at primary and metastatic sites. The consolidation phase of therapy is aimed at eliminating the remainder of disease that has survived induction chemotherapy. In most centers, this goal is achieved by administering high doses of chemotherapy supported by ASCT. Generally, external beam radiotherapy targeted at the primary tumor bed and the remaining MIBG avid sites of metastatic disease follows ASCT. Finally, treatment concludes with maintenance chemotherapy to target any remaining minimal residual disease. Maintenance therapy comprises retinoids, which induce cell differentiation, and immunotherapy targeting neuroblastoma-specific surface markers. These agents work via different mechanisms than those of conventional chemotherapy and are thought to eradicate residual clones that have acquired chemotherapy resistance. A recently completed clinical trial demonstrated the efficacy of a human-mouse monoclonal antibody Ch14.18 in improving 2-year, event-free, and overall survival. This drug, dinutuximab, gained Food and Drug Administration (FDA) approval in 2015 and is the first drug approved specifically for the treatment of high-risk neuroblastoma.

Hepatoblastoma

Hepatoblastoma is the most common malignant liver tumor in children. An estimated 150 new cases are diagnosed each year in the United States. The incidence of hepatoblastoma is slightly higher in boys than in girls, and the disease affects more white children than those of other races/ethnicities in the United States. The mean age at diagnosis is 19 months. Although most cases of hepatoblastoma are sporadic, some are associated with genetic abnormalities, including Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and trisomy 18. Hepatoblastoma has also been associated with numerous gestational factors. Children born at very low birthweight (<1,500 g) have a 20-fold increased risk of developing hepatoblastoma compared with normal-birthweight peers. Pre-eclampsia, polyhydramnios, oligohydramnios, high maternal prepregnancy weight, and infertility treatment have also been associated with an increased incidence of hepatoblastoma. Epidemiologic studies suggest that the incidence in the United States is on the rise, perhaps due to increased survival of very-low-birthweight infants.

Presentation and Diagnosis. Hepatoblastoma commonly presents with abdominal distention or palpable abdominal mass, sometimes in association with pain, fatigue, loss of appetite, and vomiting. For liver tumors, the gold standard imaging is either triphasic contrast-enhanced abdominal CT or MRI with hepatocyte-specific contrast agents such as gadoxetate disodium or gabobenate dimeglumine. The MRI provides the best assessment of the margins and vascular anatomy of the tumor. Knowledge of the extent of tumor involvement of major vessels is critical in determining resectability and for surgical planning. In addition to abdominal imaging, a chest CT is recommended because the lungs are the most common sites of metastatic disease.

In addition to imaging studies, α-fetoprotein (AFP) is a useful biomarker in the diagnosis and monitoring of hepatoblastoma. A markedly elevated AFP level suggests a diagnosis of hepatoblastoma, although concentrations of AFP may be elevated in patients with hepatocellular carcinoma, germ cell tumors, and benign liver tumors, including mesenchymal hamartoma and infantile hemangioma. Of note, elevation of AFP levels is normal in healthy infants and declines gradually until 8 months of age, rendering AFP more difficult to interpret in young children. Therefore, serial monitoring of serum AFP concentration in children younger than 1 year often is required to distinguish normal physiologic levels from abnormal elevated levels related to malignant tumors.

Histopathologic diagnosis is confirmed after obtaining a biopsy of the mass. Tissue samples may be obtained by percutaneous core needle, laparoscopic core needle, or wedge biopsy. Fine-needle aspiration is not recommended. Histologically, hepatoblastomas are generally heterogeneous tumors with combinations of epithelial, mesenchymal, and undifferentiated elements. Importantly, hepatoblastomas with pure fetal histology and low mitotic activity (up to 2 mitoses per 10 high-power fields)—approximately 7% of hepatoblastomas—have an excellent prognosis. These tumors require no further therapy if they are completely resected. Alternatively, those with predominantly small-cell, undifferentiated histology—approximately 5% of patients—carry the poorest prognosis of all histologic subtypes.

Risk Grouping and Treatment. The currently accepted staging system for hepatoblastoma describes tumor extension before any surgical treatment based on the number of involved Couinaud liver segments, vascular extension, and the presence of metastatic and extrahepatic disease. This staging system is referred to as the PRETEXT stage (prior to chemotherapy administration) and the POSTTEXT stage (posterior to neodajuvant chemotherapy treatment). Risk stratification involves use of PRETEXT, POSTTEXT, tumor histology, presence of metastatic disease, and AFP levels. However, risk group classification and treatment strategies vary among different cooperative study groups.

Complete surgical resection is required to achieve a definitive cure for hepatoblastoma. Hence, early consultation with an experienced pediatric liver surgeon is critically important. Patients who undergo a complete resection at the time of diagnosis have an excellent prognosis; however, only one-third to one-half of patients will have resectable disease at presentation. For patients with unresectable disease at diagnosis, neoadjuvant chemotherapy is administered with the goal of achieving resectability. If the tumor is not resectable after 4 cycles of chemotherapy or the tumor is located such that surgical resection will never become possible, patients are listed for orthotopic liver transplant. Complete resection, if attempted, is imperative because rescue transplant has inferior outcomes for patients with incompletely resected disease compared with patients transplanted primarily. Patients with unresectable and metastatic hepatoblastoma may be eligible for a liver transplant provided the metastases are cleared either with chemotherapy or surgical resection before transplant. Patients with resectable hepatoblastoma at diagnosis have excellent overall survival of more than 90%. For patients with unresectable disease at diagnosis but who receive chemotherapy followed by either complete surgical resection or orthotopic liver transplant, the overall survival range is approximately 60% to 80%. The outcomes for patients with metastatic hepatoblastoma have historically been poor, but survival is possible, unlike the case with many other metastatic solid tumors. Survival from pediatric cooperative group trials has ranged from 18% to 48%.

Wilms Tumor

Renal tumors account for 7% of all childhood malignancies. Most kidney cancers are Wilms tumor in young children. Approximately, 650 new cases of Wilms tumor are diagnosed each year in the United States. The incidence of Wilms tumor is slightly higher in girls than in boys, and the disease seems to occur more frequently in African American children compared with those of other races/ethnicities in the United States. The incidence of Wilms tumor seems to be similarly distributed worldwide. The mean age at diagnosis is 41 to 46 months for unilateral disease and 29 to 32 months for bilateral disease. Wilms tumor has one of the highest associations with congenital malformation syndromes. Approximately 10% of all Wilms tumors occur in settings of such anomalies. The most common congenital anomalies associated with Wilms tumor are Beckwith-Wiedemann syndrome, isolated hemihypertrophy, WAGR syndrome (characterized by the presence of Wilms tumor, aniridia, genitourinary anomalies, and mental retardation), and Denys-Drash syndrome (characterized by the development of nephropathy, Wilms tumor, and gonadal dysgenesis). Children with an increased predisposition to develop Wilms tumor should be followed closely and undergo abdominal ultrasonography every 3 months until 8 years of age. Genetic counseling should also be considered for children with the aforementioned syndromes and for patients with bilateral Wilms tumor, familial Wilms tumor, or Wilms tumor diagnosed when they are younger than 6 months.

Presentation and Diagnosis. The most common presenting symptom of Wilms tumor is an asymptomatic abdominal mass found by a parent or pediatrician (Fig 3). Approximately 40% of patients present with concomitant abdominal pain and 25% of patients develop hypertension caused by increased renin secretion. Gross or microscopic hematuria occurs in one-third of patients with Wilms tumor at presentation and it may be observed intermittently. Less commonly, patients may present with signs and symptoms of mass effect on surrounding structures, including constipation, prominent abdominal wall vessels, and congestive

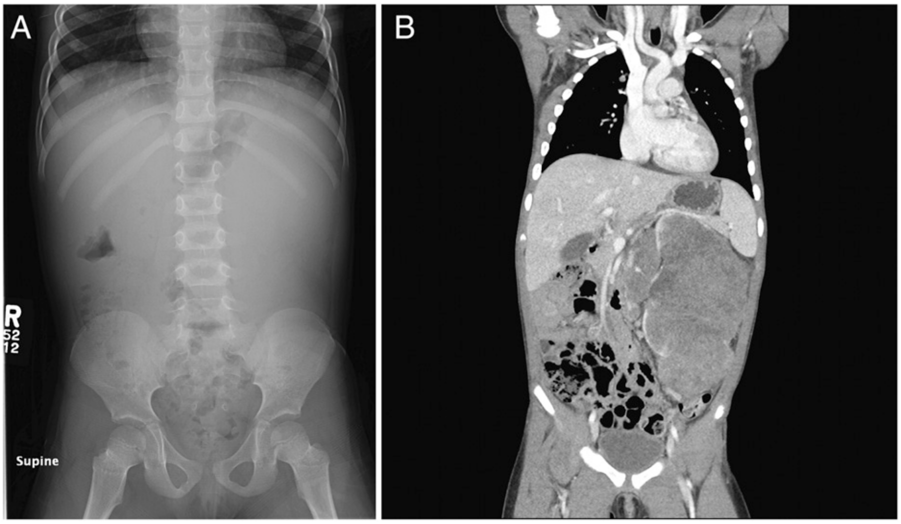

Figure 3. Abdominal radiograph (A) and computed tomographic scan (B) of the abdomen in a patient with Wilms tumor. The patient presented with intermittent gross hematuria and left flank "fullness." Notice the absence of bowel gas in the left flank due to bowel displacement by the tumor.

heart failure (due to vascular compression). Physical examination should be performed gently because Wilms tumor can be fragile and aggressive palpation of the tumor does not aid in the diagnostic evaluation. Laboratory evaluation of a suspected renal malignancy should include a complete blood cell count, renal function tests including urinalysis and electrolytes, liver function tests, and coagulation studies. Approximately 8% of patients with Wilms tumor can acquire von Willebrand factor deficiency. Abdominal ultrasonography can be performed to confirm that the mass arises from the kidney, to evaluate the contralateral kidney, and to identify intravascular tumor thrombus using color Doppler. Advanced imaging studies with enhanced contrast CT of the abdomen are indicated for evaluation of all renal tumors. A noncontrast chest CT for evaluation of pulmonary metastatic disease can be obtained simultaneously. The histopathologic diagnosis is established after radical nephrectomy either up front or after the administration of chemotherapy. Biopsy (preoperative or intraoperative) generally is not recommended because any biopsy would spread tumor cells in the peritoneum and would upstage tumor extension.

Risk Grouping and Treatment. The prognosis of patients with Wilms tumor depends on several factors such as tumor histopathology, extension of disease at diagnosis, molecular features, and the patient's age. There are 2 main staging and treatment schemas for patients with Wilms tumor. The Children's Oncology Group staging system relies on up-front radical nephrectomy with sampling of regional lymph nodes and accounts for pathologic and imaging findings; the International Society of Paediatric Oncology staging system relies on preoperative chemotherapy and local operative findings following chemotherapy. The histopathologic classification divides Wilms tumor into favorable and anaplastic histology, with favorable histology having superior outcomes compared with anaplastic histology. In addition, loss of heterozygosity on chromosomes 1p and 16q, and 1q gain are associated with inferior outcomes. The presence of 1q gain in patients with Wilms tumor with favorable histologic findings has become a powerful predictor of adverse outcome in recent clinical trials. Nonetheless, stage continues to be the stronger predictor of prognosis, with the most favorable outcomes being for patients with low-stage tumors and the least favorable outcomes for patients with metastatic or bilateral disease.

The treatment of Wilms tumor includes surgery, chemotherapy, and sometimes radiotherapy. Therefore, patients with Wilms tumor should be evaluated and treated by a multidisciplinary team of experienced cancer specialists. As mentioned previously, up-front surgical resection with sampling of regional lymph nodes is the surgical management of choice in North America. Care should be taken to avoid tumor rupture or spill during surgery. Multidrug chemotherapeutic regimens vary by stage of disease and across cooperative groups. Flank irradiation generally is reserved for patients with advanced stages and patients with anaplastic Wilms tumor. Whole-abdomen irradiation is used for patients with residual tumor or evidence of peritoneal contamination from tumor rupture or spill. Whole-lung irradiation is used for patients with anaplastic metastatic lung disease and selected patients with unresponsive metastatic disease with favorable histologic findings.

Generally, the outcome for Wilms tumor with favorable histologic findings is considered excellent. Overall survival for these patients ranges from 86% to 98% depending on the stage. The overall survival for anaplastic Wilms tumor is highly dependent on stage and ranges from 33% to 78%, with the lowest survival being for patients with distant metastatic disease. Survivors of Wilms tumor who have 1 kidney should avoid participating in contact sports with significant risks of heavy collision, such as boxing, martial arts, or football.

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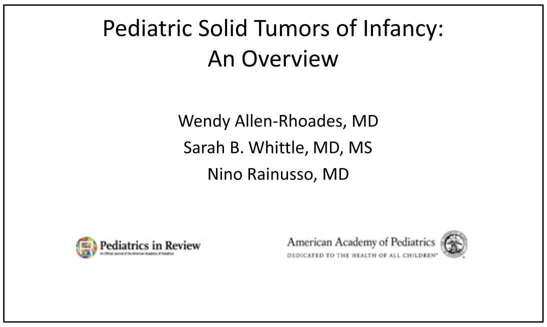
Summary

- Based on strong research evidence, solid tumors in young children compose a heterogeneous group of malignancies that present with a myriad of clinical manifestations.
- Based on some research evidence as well as consensus, cancer-related symptoms overlap with frequently occurring childhood illnesses. Common complaints in pediatric patients, such as constipation, fever, back pain, bone pain, or limping, are frequently the first signs of malignancy. The role of general pediatricians is to further investigate these symptoms when they do not resolve in a timely manner.
- Based primarily on consensus, when cancer is suspected, general pediatricians should obtain a comprehensive history, perform a detailed physical examination (including blood pressure measurement), and consider obtaining a plain radiograph of the affected body part (chest, abdomen, or limb). Patients with an abdominal mass may be initially evaluated with abdominal ultrasonography.
- Based on some research evidence as well as consensus, prompt referral to a specialized cancer center of children with suspected cancer for evaluation can prevent permanent disease sequelae and may lead to improved outcomes.
- Based on strong research evidence, pediatric solid tumors are managed by surgery, chemotherapy, and radiotherapy depending on the tumor type and stage and the patient age. Children with cancer should be offered to participate in clinical trials if it is possible. The tremendous improvement in the clinical outcome of many pediatric cancers over time has been partially achieved through patient enrollment in clinical trials. Close disease surveillance or additional genetic tests may be indicated based on the presence of congenital malformations or the tumor type.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/2/57.supplemental.



Pediatric Solid Tumors of Infancy:
An Overview

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Pediatrics in Review
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1. A 3-year-old boy is brought to the physician because the mother had noted a swelling in the abdomen last night when she was bathing him. He has been otherwise well with no bruising, weight loss, fever, or bone pain. His blood pressure is 135/88 mm Hg. Physical examination shows a well-nourished child with a palpable 8-cm mass in the right flank. A urine analysis shows 50 to 100 red blood cells. Which of the following is the most likely diagnosis in this patient?
   A. Germ cell tumor.
   B. Leukemia.
   C. Neuroblastoma.
   D. Rhabdomyosarcoma.
   E. Wilms tumor.
2. A 3-year-old boy is brought to the physician with a 3-week history of extremity pain and bruising. The mother noted that he had a swollen abdomen when she was bathing him last night. She states that he has lost weight and has had a low-grade fever. Vital signs show a temperature of 101.3°F (38.5°C), a heart rate of 115 beat/min, a respiratory rate of 18 breaths/min, and blood pressure of 108/65 mm Hg. On physical examination he is thin and in moderate distress, and bruising is noted around the eyes. The abdomen is distended, and a 10-cm right-sided mass is palpated. Which of the following is the most likely diagnosis in this patient?
   A. Germ cell tumor.
   B. Leukemia.
   C. Neuroblastoma.
   D. Rhabdomyosarcoma.
   E. Wilms tumor.
3. A 25-year-old woman with a history of bilateral retinoblastoma, for whom you have provided primary care since birth, comes to your office for counseling before decisions about having children. She has been tested and was shown to carry a germ-line mutation of the *RB1* gene. Assuming that her healthy newborn shows the presence of the germ-line mutation of the *RB1* gene on genetic testing, which of the following is the most appropriate follow-up recommendation for this family?
   A. Close surveillance by an ophthalmologist every 3 months.
   B. Dilated sedated eye examination if suspected of having a vision defect after 2 years of age.
   C. No special follow-up is indicated.
   D. Prophylactic enucleation of both eyes at the time of delivery.
   E. Routine magnetic resonance imaging (MRI) of the brain and orbits every 3 months.
4. A 5-year-old boy is brought to the physician with a 2-week history of lower back pain, poor appetite, and bruising. Over the past 3 days he has noted weakness in his legs. His mother states that he has had "potty accidents" and is encopretic. On physical examination he has normal respirations and his upper extremities have normal strength. His legs are very weak. He has no reflexes, and rectal tone is decreased. He cannot support himself to stand, and he must be carried. He has decreased sensation to touch below the umbilicus. In addition to urine and serum catecholamines, which of the following is the best next step in management for this patient?
   A. Bone scan.
   B. Elelctromyography.
   C. Electroencephalography.
   D. MRI of the spine.
   E. Physical therapy.

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5. A 2-year-old former 26-weeks premature infant is brought to the office because the mother has noted abdominal swelling and decreased appetite. Examination shows a 10-cm mass in the right upper quadrant of the abdomen. An abdominal ultrasonographic image is obtained and shows a large mass infiltrating the liver. The kidneys and suprarenal areas are normal. Laboratory studies and MRI are ordered, and results are pending. The serum level of which of the following is most likely to be significantly elevated in this patient?

   A. α-Fetoprotein.
   B. Bilirubin.
   C. Ceruloplasmin.
   D. Cholesterol.
   E. C-reactive protein.

Recognizing and Referring Children with Posttraumatic Stress Disorder: Guidelines for Pediatric Providers

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Education Gaps

Posttraumatic stress disorder (PTSD) affects approximately 4% of US children and teens and can severely impact the quality of social, academic, and personal welfare aspects of a child or adolescent and can persist into adulthood. Yet, 1 study indicated that only 18% of pediatricians surveyed felt that they had adequate knowledge of pediatric PTSD, and most (72%) reported that greater collaboration with mental health providers would improve their assessment of PTSD. (1) Health-care providers who treat pediatric populations should be aware of the magnitude of this problem and be able to screen for and refer children and teens with PTSD for specific treatments. (1)

1. Banh MK, Saxe G, Mangione T, Horton NJ. Physician-reported practice of managing childhood posttraumatic stress in pediatric primary care. *Gen Hosp Psychiatry*. 2008;30(6):536–545

Objectives

After completing this article, readers should be able to:

1. Identify and refer children affected by trauma for appropriate evaluation and evidence-based treatment.
2. Summarize the evidence for treatment approaches, including psychotherapies.
3. Understand the importance of pediatric providers knowing about what treatments have been supported for treating pediatric posttraumatic stress disorder.

CASE EXAMPLE 1

At a routine health supervision visit, a mother expresses concern that her 3-year-old daughter has “gone back to the terrible twos.” The mother says that her daughter is having intense tantrums that can last hours, is having increased difficulty separating from her, is taking much longer than usual to get to sleep at night, is often coming into her mother’s room in the middle of the night, and has wet her pants on several occasions although she was previously toilet

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ABBREVIATIONS

DSM-V	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
PTSD	posttraumatic stress disorder
SSRI	selective serotonin reuptake inhibitors

trained. The mother says that these behaviors began shortly after an armed robbery in their home a few months ago. The mother does not know whether there is any connection because she believes that her daughter is too young to understand what was going on. The mother admits that she has also had trouble sleeping and has felt "on guard." She mentions that the event may have been hard on her teenage son as well because he is staying in his room more, is spending less time with friends than usual, and has seemed touchy and irritable. *Could these be symptoms of PTSD? What recommendations could be given to this mother? How would recommendations differ for a 3-year-old and a teenager?*

PREVALENCE AND OUTCOMES OF CHILDHOOD TRAUMA

Exposure to trauma is a major public health concern that affects a vast number of children growing up in the United States. Childhood trauma encompasses a wide range of experiences that threaten the life, safety, or physical well-being of a child or loved one. Such events include child abuse and neglect, domestic violence, community violence, murder or suicide of a family member, severe accidents, and natural and manmade disasters. Epidemiologic studies estimate that as many as 70% of US children and adolescents experience some form of trauma. (1) In 2013, 679,000 children were substantiated victims of child abuse or neglect, and more than 6 million children were referred to child welfare agencies for suspected abuse or neglect. (2) A nationally representative study reported that 60% of youth aged 0 to 17 years were victims or witnesses of interpersonal violence in the preceding year. (3) This study found that 26% of youth had experienced violence in their homes. (4) Approximately 1 in 4 women and 1 in 7 men report childhood experiences of sexual abuse. (4) Rates of childhood trauma are even higher in low-income urban communities, with studies of high-risk urban youth reporting prevalences of more than 90%. (5)

In addition to well-known emotional and behavioral effects of trauma, a growing body of evidence indicates that exposure to trauma in childhood increases the risk of numerous long-term physical health problems. Medical correlates of childhood trauma include common problems such as asthma, allergies, headaches, and gastrointestinal problems, as well as many of the leading causes of death in adulthood (eg, heart disease, cancer, lung disease, kidney disease, obesity) and related health risk behaviors. (6) A recent study using biological measures found that after adjusting for age, sex, and race, court-substantiated child maltreatment predicted above-normal hemoglobin levels, lower albumin levels, poor peak airflow, and vision problems in middle-aged adults. (7) Childhood trauma is also associated with negative emotional and behavioral outcomes, including interpersonal difficulties, academic problems, delinquency, substance use, risky sexual behaviors, anxiety, depression, and suicide attempts.

Medical providers are often the first line of response to children's exposure to trauma and are in a unique position to prevent or reduce long-term consequences. (8) Although well-established treatments are available, children exposed to trauma often do not receive these treatments. Barriers to seeking help include limited access to mental health services, few providers with experience treating trauma in many communities, and the stigma associated with mental health. In addition, parents may not be aware of symptoms associated with trauma or the profound effects that trauma can have on children of all ages. Pediatric and adolescent medicine doctors are in a unique position to increase access to care because they are often trusted adults with whom youth feel safe discussing traumatic experiences that they are afraid or ashamed to disclose, such as child abuse or domestic violence. (8) Moreover, pediatric care settings are well suited for providing education, monitoring, and referrals for trauma-exposed children and their families.

POSTTRAUMATIC STRESS DISORDER

Although children may evidence a range of reactions to trauma, posttraumatic stress disorder (PTSD) represents the most direct and systematic pattern of symptoms resulting from traumatic exposure. This impairing condition involves persistent distress or fear, avoidance of traumatic memories or reminders, and significant alterations in mood, thinking, and behavior. Also, PTSD is an important predictor of long-term mental and physical health outcomes. However, not all children develop PTSD, and many are able to recover from a traumatic event with few consequences. The reported numbers of trauma-exposed children who develop PTSD vary widely across studies of different populations, types of trauma, and proximity or extent of impact. For example, studies of children affected by disasters have reported rates as low as 10% in New York school-age children after the World Trade Center attacks to as high as 86% in children in South Florida after Hurricane Andrew. (9) Thus, all children exposed to traumatic events warrant screening for trauma-related symptoms and impairment.

DSM-V CRITERIA FOR PTSD

Released in 2013, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* made substantial changes to the diagnostic criteria for PTSD. First, recognizing the broad range of symptoms resulting from trauma, PTSD has been moved from the section of "anxiety disorders" to a new category of "trauma and stress-related disorders," including acute stress disorder and the adjustment disorders. Second, the definition of events that qualify as traumas has been expanded to explicitly include indirect or vicarious exposure, such as hearing about the violent death of a close relative or friend or repeated exposure to aversive details through professional duties (eg, first responders). Third, the requirement that a trauma results in reported or observed fear, helplessness, or horror has been removed because this criterion was found to be difficult to assess and unreliable in predicting significant traumatic reactions or impairment.

To qualify for a diagnosis of PTSD, symptoms in each of 4 categories must be present for at least 1 month, although onset can occur at any time after experiencing a trauma. Symptoms must also cause significant distress and/or impairment of functioning. The four symptom clusters are: 1) intrusive thoughts, memories, or emotions, which include dreams and flashbacks related to the trauma; 2) avoidance of stimuli associated with the trauma; 3) negative thoughts, beliefs, or emotions associated with the trauma; and 4) alterations in arousal and reactivity, including angry outbursts, self-destructive behaviors, hypervigilance and exaggerated startle response, concentration difficulties, and sleep disturbance. (10) Acute stress disorder is diagnosed when symptoms are present for 3 days to 1 month after a trauma and cause significant impairment. It should also be noted that the *DSM-V* has added a preschool subtype of PTSD for children 6 years and younger. In addition, many children who do not meet the full criteria for the *DSM-V* diagnosis may present with significant and impairing subthreshold symptoms and, thus, are in need of treatment.

ADDITIONAL SIGNS AND SYMPTOMS OF TRAUMA IN CHILDREN

Although the *DSM-V* provides an expanded set of criteria for PTSD that better captures the broad range of symptoms that can result from trauma, including a modified set of criteria for young children, additional behavioral changes might indicate trauma-related impairment and warrant referral for a specialized evaluation. Specific reactions to trauma (including PTSD symptoms) often look different at different ages due to developmental norms and changes. The effects of trauma can present as regression in, or disruption of, key developmental tasks at a particular age. In infants, trauma could result in difficulties with trust and reliance on caregivers, constant crying and inability to be soothed, sleep and feeding problems, and regression in previously attained language and motor skills. Toddlers may have difficulty separating from parents, become clingy with or avoidant of caregivers, exhibit overactive or underactive behavior, and develop problems sleeping, eating, or toileting. They may also show changes in mood such as increased irritability, inconsolable crying, severe aggression, or intense fear. Similarly, in preschool children, trauma reactions can manifest as regression in previously acquired language, cognitive, and motor skills (eg, babyish talk or behavior); toileting difficulties; and temper tantrums. Preschool children may also exhibit difficulties with peers and are typically the youngest to report nightmares related to the trauma or other themes. In school-age children, besides the core symptoms of PTSD, traumatic reactions often include declining grades, overdependence on caregivers or other adults, generalized worries and fears, depression, inattention, and conduct problems. Adolescents are at particular risk for eating disorders, pain or other somatic problems, low self-esteem, depression, interpersonal difficulties, risky sexual behaviors, delinquent behaviors, and substance problems. Considering the effects of trauma in this developmental perspective can help identify children and adolescents who may not clearly fit the *DSM* criteria for PTSD but who are nonetheless experiencing the effects of a traumatic experience.

It is also important to consider that the effects of trauma can mimic other behavioral health problems. Because of this, youth are often misdiagnosed and do not receive appropriate trauma-focused treatment. For example, regression in developmental milestones in a young child exposed to trauma could be mistaken for a developmental delay or autism spectrum disorder if a thorough developmental history and a trauma assessment are not conducted. As another example, difficulties with concentration and attention are typical symptoms of trauma in school-age and adolescent youth but could be misdiagnosed as attention-deficit/hyperactivity disorder. However, the first-line pharmacologic treatments for attention-deficit/hyperactivity disorder (psychostimulants) can potentially exacerbate trauma-related symptoms and even lead to hallucinations. Moreover, if the trauma goes unaddressed, initial symptoms can develop into long-lasting mental and physical health problems.

PREVENTIVE INTERVENTIONS

Factors that predict or buffer against PTSD are not entirely understood. However, negative outcomes in children, including PTSD, tend to be exacerbated when caregivers are involved in or affected by the trauma (eg, domestic violence, death of a parent, child abuse), the trauma results in disruption or loss of possessions (eg, a house fire), and the trauma is chronic or the threat to safety is ongoing (eg, child abuse or neglect, community violence). Thus, interventions in the aftermath of trauma can reduce the likelihood of PTSD and other important problems by taking these factors into account. First, involving and supporting caregivers is critical to enhancing children's recovery from a trauma. Parents benefit from knowing how to talk to and support their children. Parents may also be in need of treatment to address their own reactions to a traumatic event. If the trauma involves the loss of a parent, efforts to support the role of an existing caregiver are crucial. Second, minimizing disruption to a child's life can reduce the impact of the trauma. Parents may wish to move to a new home or neighborhood after a traumatic event, but this may not always be the most helpful for a child's recovery. Parents may also want to keep children home from school. However, a return to normal routines, including school, can support recovery. In cases of child abuse and neglect, child welfare agencies may remove children from their homes and caregivers to ensure safety. Unfortunately, this kind of disruption can exacerbate traumatic reactions, and children are too often revictimized in foster and group homes. Finally, immediate responses to trauma require preventing ongoing or recurrent trauma. However, as noted previously herein, ensuring the safety and security of a child and family sometimes results in disruption, and, therefore, these goals should be balanced to maximize a child's safety while reducing disruption as much as possible. Additional protective factors for children exposed to trauma include a supportive school environment where the child feels connected and engaged, community resources, supportive peer relationships, and child characteristics such as self-esteem, coping skills, self-efficacy, interpersonal skills, and academic success. On the other hand, children with preexisting histories of depression or anxiety, previous trauma, and poor coping skills (eg, rumination about negative events) are more vulnerable to developing PTSD.

SCREENING MEASURES

A pediatrician can routinely screen for traumatic exposure by asking a simple question at all health supervision visits: "Since the last time I saw you, has anything really scary or upsetting happened to you or your family?" Parents of young children can be asked an analogous question, "Since the last time I saw your child, has anything really scary or upsetting happened to your child or anyone in your family?" (8) Responses to this question can be used to determine whether the child has experienced a trauma as defined previously herein. Many children and parents may also report nontraumatic stressors, such as the loss of a pet or a friend moving away. Validated screening measures are also available, such as the 15-item Traumatic Events Screening Inventory and a parent-report version adapted for young children. (11)

To assess for the presence of PTSD in children who have experienced a traumatic event, a provider can administer a brief symptom screen. The Child Stress Disorders Checklist–Short Form is a 4-item measure that has demonstrated reliability in screening for *DSM-IV* PTSD symptom clusters. (12) An abbreviated 9-item version of the UCLA PTSD Reaction Index is also available for screening *DSM-IV* symptoms. However, as of the writing of this article, brief screeners have not yet been adapted to correspond to the expanded *DSM-V* criteria. The full UCLA PTSD Reaction Index has been revised for *DSM-V*. This measure assesses preliminary diagnostic information and frequency of symptoms in children older than 6 years with 27 questions assessing core symptoms of PTSD (eg, "I feel like I am back at the time when the bad thing happened, like it's happening all over again," "I try to stay away from people, places, or things that remind me about what happened") and 4 additional items assessing dissociative symptoms (eg, "I feel not connected to my body, like I'm not really there inside"). (13) Caregiver reports are most appropriate for young children, such as the parent-report version of the UCLA PTSD Index or the PTSD Symptoms in Preschool Children scale. (14) Information about additional screening and assessment measures is available through the National Child Traumatic Stress Network (http://www.nctsn.org/resources/online-research/measures-review) and the National Center for PTSD (http://www.ptsd.va.gov).

EVIDENCE-BASED TREATMENTS FOR PTSD IN CHILDREN

Numerous treatments have been developed for treating PTSD in children and adolescents, and many of these treatments have been supported with empirical evidence (see http://www.nctsn.org/resources/topics/treatments-that-work/promising-practices). The following discussion highlights a selection of treatments that have received substantial research support from multiple clinical trials or that are promising approaches for specialized populations of trauma-exposed youth. Trauma-focused interventions for children and adolescents are most effective in treating the core symptoms of PTSD and tend to share several common elements: 1) parental involvement, ranging from extensive for young children to minimal for adolescents; 2) coping skills training to manage traumatic reactions; 3) mastery of avoided situations or activities associated with the trauma; and 4) structured retelling of the trauma through creation of a narrative in collaboration with a specially trained therapist. Exposure to traumatic reminders, both in vivo and through creation of the trauma narrative, is encouraged to desensitize children to reminders of the trauma, contextualize the trauma as 1 past event in the child's life, and help children cope with emotions and thoughts linked to traumatic memories. The recommended treatments described later herein all combine a structured therapist-guided approach in conjunction with a collaborative relationship with the child and family.

Early Childhood

Effective interventions with young children focus on the parent-child dyad rather than treating children individually. Child-Parent Psychotherapy (CPP) is designated a well-supported and efficacious treatment for PTSD and other symptoms related to trauma in children 6 years and younger (including infants and toddlers). Drawing on psychodynamic, attachment, trauma, cognitive behavioral, and social learning frameworks, CPP addresses children's reactions to trauma though the parent-child relationship. Children are seen with a primary caregiver (generally mothers) in sessions that focus on affect regulation, changing maladaptive behaviors, supporting developmentally appropriate interactions and activities, and guiding the parent and child in creating a joint trauma narrative. Child-Parent Psychotherapy has been supported in 3 randomized controlled trials with ethnically and racially diverse families, primarily of low socioeconomic status, affected by child maltreatment and domestic violence. Follow-up has indicated that reductions in child and maternal mental health symptoms are retained over 6 months. (15)

Parent-Child Interaction Therapy (PCIT) is another intervention that focuses on the parent-child relationship to reduce behavioral problems in children. (16) It is a highly structured treatment in which the therapist coaches the caregiver during play interactions with the child through use of a 1-way mirror and earbuds. The caregiver learns skills for responding to the child, implementing effective discipline, and increasing compliant behavior. A well-established treatment for oppositional and aggressive behavior problems in children, PCIT has received more recent support as a promising treatment for reducing behavior problems in abused and neglected children. It has also been found to reduce caregiver stress and repeated incidences of maltreatment by parents who have abused their children.

School-Age Children

Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) has received the most empirical support for the treatment of PTSD in culturally diverse school-aged children and adolescents affected by a range of traumatic experiences, including sexual and physical abuse, domestic violence, traumatic grief, disasters, and terrorism. (17)(18) Numerous clinical trials have supported the efficacy of this treatment in reducing PTSD and other emotional and behavioral symptoms related to trauma in children and adolescents of diverse racial, ethic, socioeconomic, and cultural backgrounds. Trauma-Focused CBT is a stepwise approach that involves psychoeducation about the effects of trauma, teaching children skills for coping with traumatic experiences and symptoms, developing safety skills, gaining exposure to and processing of the traumatic experience through construction of a narrative, and gaining exposure and habituation to traumatic reminders. Trauma-Focused CBT also involves psychoeducation and support for parents and conjoint parent-child sessions during which the child is able to share her or his trauma narrative. Although it follows a manualized sequence of steps, activities within each step can be flexibly tailored to the needs and developmental stage of the child. For example, in young children the trauma narrative can be created through use of puppets or drawing, whereas an older child typically creates a written narrative.

Cue-centered treatment (CCT) (19) was developed to address PTSD and other trauma-related symptoms in children who have experienced long-term, ongoing trauma and other adversities. It recognizes that children with multiple traumatic experiences (or complex trauma) may gain limited benefits from processing a focal trauma. This treatment focuses on helping the child to become his or her own agent of change through increased awareness of trauma-related experiences and symptoms; development of skills for coping with trauma symptoms; and increased insight into relationships among traumatic experiences, emotional reactions, and behavioral responses. Although CCT remains an emerging treatment, the first randomized controlled trial with 65 youth with histories of interpersonal violence exposure found that compared with a waitlist control condition, CCT was associated with a greater reduction in PTSD and anxiety symptoms, and improvement in overall functioning. These gains were maintained over a 3-month period after treatment. (19)

Cognitive Behavioral Interventions for Trauma in Schools (CBITS) is a promising approach to addressing trauma in the school setting using a group treatment model with elements similar to TF-CBT. Because the program is administered in schools, teacher education about the effects of trauma is included, and there is a parent psychoeducation component. Advantages of CBITS are that school-based treatment can be made available to children who may not otherwise have access to treatment, and participating in a group at school may reduce the stigma associated with obtaining mental health services outside the school environment. In addition, peer support and modeling is facilitated through the group format. The most significant disadvantage is that treatment cannot be tailored to individual children's symptoms, and certain kinds of trauma (eg, sexual abuse) may not be appropriate for a school-based group format. Cognitive Behavioral Interventions for Trauma in Schools is most suited for addressing PTSD and other symptoms associated with exposure to domestic or community violence in underserved youth who are unlikely to access clinic-based mental health services. It was developed through a collaborative partnership with schools and community members (including parents) and has been supported in randomized clinical trials and a quasi-experimental trial. These studies found reductions in PTSD and depressive symptoms in elementary and middle school children participating in the treatment compared with a control group. The developers report success in implementing CBITS in numerous communities with students from diverse racial, ethnic, and socioeconomic backgrounds. (20) They have now developed an adaptation that can be delivered by non–mental health–trained school staff. A small randomized trial indicated modest improvements in trauma-related symptoms.

CASE EXAMPLE 2

Before a camp physical, the parents of a 14-year-old girl tell her pediatrician that she has "been especially hard to connect with" in the past several weeks. They say that she has a new group of friends, has felt pressure to "fit in," and is struggling with her body image. The parents say that these behaviors began shortly after a party last month, where several parents described a house with "no parental supervision, and where several kids left the party looking sick or high." They worry that she may have been date raped because of specific references in online postings and that she becomes very tearful at the mention of a boy in school with whom she went to the party. The teen girl admits to having trouble sleeping and to feeling "empty and hopeless." She mentions that she has even thought about suicide, but "that would be a cop-out." *Could these be symptoms of PTSD? What recommendations could be given to this patient and these parents?*

Adolescents

In addition to the treatments described previously herein for school-age children, which are also appropriate for teens, 2 additional interventions modified from adult treatments may be appropriate for adolescents affected by trauma. Prolonged Exposure Therapy for Adolescents (PE-A) has been adapted from a well-established adult protocol to meet the developmental needs of teens (eg, increased case management and relapse prevention). It includes psychoeducation about the effects of trauma, training in breathing techniques to manage distress associated with traumatic reminders, exposure to avoided situations or activities associated with the trauma, and repeated retelling of the traumatic memory during sessions. Although parent participation in psychoeducational sessions and in supporting in vivo exposure is encouraged, it is not essential for treatment success. Two randomized controlled trials have found that PE-A resulted in a greater reduction in PTSD and depressive symptoms compared with a control treatment in adolescent girls with PTSD related to sexual abuse (21) and in adolescents with PTSD related to various single-event traumas. (22) Prolonged Exposure Therapy for Adolescents is likely most appropriate for older teens who have experienced a discrete or single-event trauma, such as a sexual assault or a motor vehicle accident.

Dialectical Behavior Therapy (DBT) has been adapted for use with teen populations from a well-established adult treatment for suicidal and other self-harming behaviors and, thus, may be a beneficial approach for adolescents exhibiting these kinds of symptoms in response to trauma. Dialectical Behavior Therapy combines cognitive and behavioral therapy with Eastern practices, such as mindfulness, to help teens develop skills for coping with intense, or dysregulated, emotions in healthy ways and to reduce self-harming behaviors. An intensive treatment, DBT for adolescents involves individual therapy, a 12-week skills group including parents or other family members, telephone coaching between sessions, and a consultation group for therapists. Although limited research has been conducted with adolescents, 1 randomized clinical trial found greater decreases in self-harm, suicidal ideation, and depression in adolescents participating in DBT compared with a control treatment. (23) Self-harming behaviors and suicidal ideation are often associated with trauma in teens, and 1 small study with adolescent girls reported a significant reduction in trauma-related symptoms after completion of DBT. (24)

Other Treatments that Have Limited Support or Are Not Recommended

Many treatments provided to traumatized children have not been adequately studied or have found been to be harmful. For example, ambiguous results have been found for psychological debriefing during which children share traumatic experiences and reactions and receive empathetic support and psychoeducation in the immediate aftermath of a trauma. Unstructured, child-directed play therapies have also been found to have limited benefits compared with structured approaches such as those described previously herein. At the other end of the spectrum, restrictive rebirthing or holding techniques that are sometimes believed to relieve symptoms of trauma are found to be harmful and can result in injury or death.

Psychopharmacologic Treatments

Because pediatric PTSD is developmentally distinct from adult PTSD, (8)(25)(26) evidence for pharmacotherapy is limited for the core symptoms of PTSD, and treatment should be reserved for cases in which symptoms are so severe that a child cannot participate in psychotherapy or other forms of therapeutic support or when impairing comorbid symptoms are present and severe enough to be a focus of treatment. (25) "In these instances, pharmacotherapy targets specific symptoms affecting the child with PTSD (e.g., disrupted sleep, nightmares, hypervigilance, new-onset generalized anxiety, *etc*.). Since high quality drug trials in pediatric PTSD are sparse, pharmacologic agent selection should be guided by the following factors: 1) existing reports in the literature, 2) known tolerability for other pediatric indications or 'off label' uses, and 3) the agent's mechanism of action and the neurobiological theory for the symptoms expressed. To a lesser extent, cautious extrapolation of adult PTSD evidence may be considered, as long as side effects are monitored for closely." (25) The reader is referred to thorough reviews (see references) to learn more about how medication management can be used in conjunction with evidence-based psychotherapy in cases in which prolonged and severe symptoms or conditions (eg, depression, anxiety, psychosis) warrant pharmacotherapeutic intervention. (8)(25)(26) Emerging evidence exists for a variety of agents, including tricyclic antidepressants, selective serotonin reuptake inhibitors, α-adrenergic agents, prazosin, propranolol, second-generation antipsychotics (risperidone, quetiapine), and mood-stabilizing agents (carbamazepine, divalproex). (26) At of the time of this writing, however, all medications listed previously herein are still considered off label for pediatric patients. And, importantly, these agents should be used primarily as an adjunct to high-quality psychotherapy by skilled providers.

Traumatized children and teens are especially overrepresented in the child welfare and juvenile justice systems. Cohen and colleagues (27) advise practitioners in the field to promote integrated and trauma-informed systems of care by being attuned to "early identification and appropriate referral to trauma-focused treatment via 'any available door' through which youth enter child-serving systems. This includes the educational, primary care, child welfare, juvenile justice, or mental health systems, … especially as children move from one system to another."

CONCLUSION

Although many children and adolescents are resilient after traumatic experiences, others develop a variety of emotional and behavioral symptoms that can be severe and long-lasting.

Pediatric providers are in a unique position to identify children and adolescents exposed to trauma and to facilitate prevention and treatment of PTSD and other trauma-related conditions. Because of their role as trusted adults and their routine contact with children and families, pediatricians may be the first line of response for many traumatized children. Thus, screening for traumatic exposures and having access to tools for screening symptoms of PTSD can be crucial components of routine care. For children at risk or who are exhibiting major trauma-related symptoms, recommended treatments generally use a structured skills-based approach, involve parents, and support children in developing coping strategies and mastery of traumatic triggers. Primary care providers may begin the process of recovery with education about the effects of trauma, monitoring of symptoms, support for families, and referral for specialized services. To facilitate referrals, practitioners should become familiar with trauma treatment options that meet the criteria described previously herein and are available in the local community. Leaders in the field of pediatric PTSD have advocated the following for all child-serving professionals: 1) early and effective identification of trauma and its impact in pediatric populations; 2) evidence-based, trauma-focused psychotherapeutic interventions; 3) evidence-based psychopharmacologic treatments for traumatized children (when they become available); 4) integrated, trauma-informed systems of care; 5) collaboration between primary care and child and adolescent psychiatry. (Crucial to the role of primary care is to know *when* to refer and *what sort of treatment* to refer to. Recent literature has underscored the need for dissemination and availability of psychotherapies that work for these vulnerable populations.); and 6) training the next generation of pediatric providers about each of the previous items. (27)(28)

Summary

1. Strong evidence indicates that a large number of children and adolescents in the United States (as many as 70%) experience trauma, with significant effects across psychological, emotional, and behavioral functioning. (1) Pediatric primary care providers are well positioned to intervene to support youth affected by trauma and to refer them to evidence-based treatments.
2. Professional consensus supports the use of simple screening questions to ask about trauma during routine pediatric appointments, (8) and use of well-established measures of trauma exposure and symptoms, such as the UCLA PTSD Reaction Index, are also available. (13)
3. Strong research evidence and professional consensus suggests that the most effective psychotherapies for treating PTSD in children and teens incorporate parental involvement, coping skills training, mastery of avoided trauma reminders, and structured exposure to traumatic memories through creating a narrative with a specially trained therapist (see http://www.nctsn.org/resources/topics/treatments-that-work/promising-practices). For young children, Child-Parent Psychotherapy is a well-established treatment with strong research support, (15) and Parent-Child Interaction Therapy is a promising intervention with some early research support for treating behavior problems in abused and neglected children. (16) Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) is a well-established treatment, with strong research support, for school-age children and adolescents. (17)(18) Cue-Centered Treatment is a newer intervention with initial research support for treating trauma-related symptoms in children and adolescents and may be particularly effective for youth with repeated or long-term trauma exposure. (19) Cognitive Behavioral Interventions for Trauma in Schools is a promising approach, with modest research evidence, for addressing trauma in the school setting using a group treatment model with elements similar to TF-CBT. (20) In addition, Prolonged Exposure Therapy for Adolescents, adapted from a well-established treatment for adults, has moderate research support for treating single-event traumas in adolescents. (21)(22) Dialectical behavior therapy has received support from 1 small study with adolescent girls. (24)
4. Evidence for the use of pharmacotherapy in treating symptoms of trauma in children and adolescence is limited, and, therefore, medication treatment is recommended only in cases in which symptoms are so severe that a child cannot participate in psychotherapy or other forms of therapeutic support, or when impairing comorbid symptoms are the focus of treatment. (25)
5. In settings where recommended treatments are not available, providers can consult a toolkit created by the National Child Traumatic Stress Network for additional resources on supporting children and families affected by trauma (https://www.healthcaretoolbox.org/).

References for this article are at http://pedsinreview.aappublications.org/content/39/2/68.

PIR Quiz

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1. A mother and her 2-year-old daughter were asleep in their home when there was a gas explosion. Both mother and child were hospitalized for burn injuries. You see the girl in the clinic 6 weeks after her injury. Her burns are healing well, but she has ongoing wound care. Although she had been sleeping through the night before her injury, she now wakes up in the early morning hours screaming, and it is difficult to calm her. It is impossible to calm her when she is taken to doctor visits, and she screams throughout visits, even when she is not touched and there are no painful medical interventions. You review the criteria for a diagnosis of posttraumatic stress disorder (PTSD) and note that there are 4 symptom areas that are required for a diagnosis. Which of the following PTSD diagnostic criteria is most consistent with the sleep concerns in this patient?
   A. Alterations in arousal and reactivity.
   B. Avoidance.
   C. Exposure to death or threatened death.
   D. Intrusion.
   E. Negative alterations in cognitions and mood.
2. A 6-year-old boy was in a motor vehicle collision in which his father was killed. The boy had abrasions, but no major injuries. He sees you for a visit a week after the collision and several days after his father's funeral. He is a good student and plays soccer on his school team. His mother asks you for advice on how to support his emotional health after his injury. Which of the following measures is the most effective in supporting recovery in this patient?
   A. Begin an antidepressant.
   B. Continue to participate on his soccer team.
   C. He and his family should move to a new home.
   D. Participate in counseling without his mother.
   E. Stay home from school with his family for a month.
3. A 7-year-old girl was separated from her family during a hurricane. She stayed at school for 24 hours with several teachers and students who were separated from their families. Her home was flooded and she and her family lived in a Red Cross shelter for several weeks. They are now sleeping on the floor of a family member's home. The girl has had sleep disturbance, cries easily, does not want to see her home, and asks her mother several times a day whether the house they are in will flood as well. Which of the following is the most appropriate management strategy for this patient's symptoms?
   A. Change of school setting.
   B. Individual psychotherapy.
   C. Medication to help her sleep.
   D. Psychotherapy for her and at least 1 of her parents.
   E. Psychotherapy for the parents alone without her.
4. A 16-year-old girl was raped at a party after a football game. Pictures were taken of the incident, and these photographs were shared at school. She has begun cutting herself, and her self-injurious behavior became obvious to her parents. They bring her to you for advice on how to support her in her recovery from this experience. Which of the following is the best next step in the management of this patient?
   A. Antidepressant medication.
   B. Child-Parent Psychotherapy.
   C. Dialectical Behavioral Therapy.
   D. Psychological debriefing.
   E. Sending her away to live with relatives.

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5. A 10-year-old boy has been diagnosed as having PTSD after recurrent episodes of physical abuse perpetrated by his father. His mother has found support in her church community, and several of the church parishioners have recommended a rebirthing “holding” ceremony to alleviate this boy’s symptoms. The mother asks your opinion. Which of the following is the most appropriate intervention you would recommend for this patient?
    A. Child-directed play therapy.
    B. Child-Parent Psychotherapy.
    C. Proceed with the rebirthing “holding” ceremony.
    D. Psychological debriefing.
    E. Trauma-Focused Cognitive Behavioral Therapy.

Kawasaki Disease

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Education Gap

Kawasaki disease is the leading cause of acquired heart disease in developed countries. A rare disease without pathognomonic findings or a diagnostic test, Kawasaki disease should be considered in the differential diagnosis of a child with prolonged fever.

Objectives After completing this article, readers should be able to:

1. Recognize the clinical findings associated with Kawasaki disease (KD).
2. Formulate a differential diagnosis for patients with suspected KD.
3. Describe the laboratory values typically seen in KD.
4. Discuss the role of echocardiography in the management of patients with KD and describe the cardiac complications of the disease.
5. Define the primary treatment of KD with intravenous immunoglobulin and oral aspirin.

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ABBREVIATIONS

ASA	aspirin
CAL	coronary artery lesion
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
LAD	left anterior descending artery
RCA	right coronary artery

CASE STUDY

A 3-year-old previously healthy Hispanic girl is brought to her pediatrician's office by her mother with a history of 6 days of fever. The fever has been present daily and unremitting despite administration of antipyretic medications. She has been irritable, with decreased appetite. Her mother noticed an erythematous nonpruritic rash covering her torso 1 day after fever onset. She has developed red eyes in the past 2 days. She has no siblings and attends child care.

On examination she is febrile to 102°F (38.9°C) and tachycardic at 140 beats/min. Her blood pressure while crying is 110/60 mm Hg. Her weight is 32 lb (14.5 kg). She has conjunctival injection with limbal sparing and without exudate. Her lips appear erythematous and cracked, and her oropharynx is diffusely erythematous without exudates. She does not have substantial cervical chain lymphadenopathy. A polymorphous maculopapular rash covers her torso and extremities. The dorsum of her hands and feet appear swollen.

On laboratory examination she has a total white blood cell count of $15.6/\mu L$ ($\times 10^9/L$)*, her hemoglobin level is 9.8 g/dL (98 g/L), and her platelet count is* $669{,}000 \times 10^3/\mu L$ ($\times 10^9/L$)*. The differential count of the white blood cells is 81% neutrophils and 14% lymphocytes. She has mild elevation of her transaminase values, with an alanine aminotransferase level of 68 U/L (1.14* μ*kat/L) and a normal aspartate aminotransferase level. Her C-reactive protein (CRP) level is 98 mg/L*

(933 nmol/L), and her erythrocyte sedimentation rate is 65 mm/hour. There are 25 white blood cells per high-power field on urinalysis.

OVERVIEW

Kawasaki disease (KD) is an acute febrile illness of childhood that is characterized pathologically by vasculitis of medium-sized, extraparenchymal arteries, with a predilection for the coronary arteries. It is the leading cause of acquired heart disease in developed countries, whereas rheumatic heart disease continues to dominate the developing world. The natural history, treatment, and sequelae of untreated KD are now well described. However, the etiology remains obscure, hampering efforts to develop a diagnostic test and targeted treatments.

In the absence of a diagnostic test, KD remains a diagnosis based on clinical criteria. All signs and symptoms of KD resolve after the acute illness (even in the absence of treatment), but coronary artery lesions (CALs) develop in 3% to 5% of children treated with intravenous immunoglobulin (IVIG) and in up to 25% of untreated children. The prognosis of the disease hinges entirely on the presence and severity of CALs, which can range from mild dilatation to giant aneurysms (Fig 1). It is unclear at this time whether children who have normal-appearing coronary arteries during the acute phase of the disease will be at risk for endothelial dysfunction and accelerated atherosclerosis later in life.

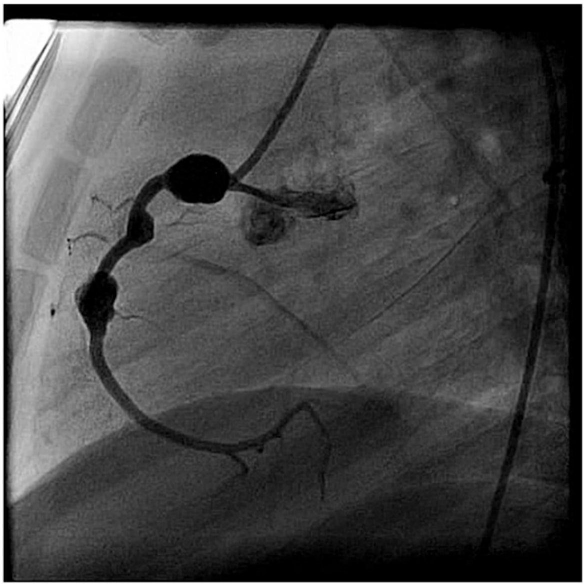

Figure 1. Selective right coronary angiogram demonstrating multiple aneurysms in a child with Kawasaki disease.

EPIDEMIOLOGY

Kawasaki disease was first described in 1967 by a Japanese pediatrician, Dr Tomisaku Kawasaki, as *mucocutaneous lymph node syndrome*. At that time, the cardiac involvement of KD was not apparent, and neither was effective treatment described. Within a few years, autopsy cases of patients with KD demonstrated coronary artery aneurysms and thrombosis, and the cardiac complications of KD became evident. Since Dr Kawasaki's initial report, KD has been described in children around the world and in virtually all races. However, children of Japanese ancestry are at highest risk for KD.

Since 1970, Japan has collected epidemiologic data about KD nearly every 2 years via nationwide surveys. Interestingly, although the birth rate has declined, the numbers of patients diagnosed as having KD and the incidence rate in Japan have risen rapidly since the 1990s. There have been 3 documented epidemics of KD in Japan, in 1979, 1982, and 1986. In 2012, the incidence rate of KD in Japan was 264.8 per 100,000 children aged 0 to 4 years, which exceeds the highest rate during any of the epidemics and is the highest rate recorded. The reason for the linear increase in the incidence rate of KD in Japan is unclear. Fortunately, the proportion of patients with coronary artery aneurysms and myocardial infarction has decreased from 6% in 1999-2000 to 2.8% in a recent survey. (1) In contrast to Japan, hospitalization rates associated with KD in the United States have been relatively stable for the past decade. The hospitalization rate in 2006 was 20.8 per 100,000 children younger than 5 years, and it was 19 per 100,000 children younger than 5 years in 2009. (2) Most hospitalizations occurred in children younger than 3 years. Children of Asian/Pacific Islander descent had the highest hospitalization rate, demonstrating the likely role of genetics in the pathogenesis of KD. An underlying genetic predisposition is further supported by the findings that siblings of children with KD in Japan have a 10-fold increased risk of the disease, and the parents of children with KD in Japan today are twice as likely, compared with other adults, to have had KD when they were children.

Risk factors for poor coronary artery outcomes have been studied in several populations. Demographic factors such as young age (particularly <6 months and >9 years), male sex, Asian and Pacific Islander race, and Hispanic ethnicity have been associated with poor clinical outcomes. Laboratory parameters such as neutrophilia, thrombocytopenia, hyponatremia, elevated CRP level, and elevated transaminase levels have all been associated with poor response to IVIG and/or the development of CALs. (3) Fundamentally, patients with evidence of substantial and widespread inflammation are at highest risk.

PATHOGENESIS

The etiology of KD remains unknown. Many aspects of KD mimic infectious processes, such as toxin-mediated illnesses and viral illnesses. Seasonal peaks have occurred in the United States and in Japan, with an increased incidence in localized areas, suggesting a transmissible vector. Researchers have looked painstakingly and unsuccessfully for an etiologic infectious agent, including Epstein-Barr virus, adenovirus, human coronavirus, human bocavirus, *Yersinia pseudotuberculosis*, herpes viruses, and others.

Toxins, such as those produced by *Staphylococcus aureus* or *Streptococcus pyogenes,* have been postulated as the etiology of KD because the rash can appear similar to an erythroderma, similar to that in toxic shock syndrome or streptococcal toxic shock syndrome. In addition, the efficacy of treatment with IVIG could be explained by immunoglobulin binding of toxins, although antigen-independent mechanisms have been postulated as well. Toxins act as superantigens, which nonselectively activate large numbers of T cells, leading to massive cytokine release and inflammation. Studies looking at the role of superantigens in KD have been conflicting. Specifically, isolation of superantigen-producing organisms, isolation of superantigen proteins, and the presence of an immunologic signature of superantigen activity have varied across studies.

To date, no unique agent has been proven to cause KD. An alternative hypothesis posits that many infectious agents trigger a final common pathway in genetically susceptible hosts, which is supported by the finding that many patients diagnosed as having KD have documented concomitant infections. The interplay of infection and vascular inflammation has been described in other forms of vasculitis, such as hepatitis B and polyarteritis nodosa, hepatitis C and cryoglobulinemia, and staphylococcus and Wegener granulomatosis. Accordingly, the hypothesis that infectious agents may trigger the inflammatory cascade in KD has face validity.

Both the innate and adaptive arms of the immune system have been evaluated in the pathogenesis of KD. The innate immune system includes epithelial barriers and phagocytic cells that provide protection against infection, whereas the adaptive immune response is mediated by antigen-specific lymphocytes stimulated by infectious agents. There is evidence that the innate immune system plays a significant role in the pathogenesis of KD. A study reported that neutrophils are important actors in the initial attack on coronary artery walls. In a murine model of coronary arteritis induced by *Lactobacillus casei* cell wall extract, Toll-like receptor 2 and its downstream adaptor protein, MyD88, are required for the development of CALs, establishing a role for the innate immune system. Furthermore, there is evidence that interleukin-1β plays a highly important role in the development of CALs in the murine model of KD. In addition, multiple studies have demonstrated increased expression levels of innate immunity-associated genes and transcriptional profiles during the acute phase of KD. T cells also play an important role in KD. CD8+ T cells have been found in coronary arteries from autopsy specimens. Studies of acute and subacute sera in patients with KD showed a decrease in the population of regulatory T cells in the acute phase, with normalization after treatment with IVIG, indicating that impaired immunoregulation has a possible role in the development of KD.

Genome-wide association studies have described functional single nucleotide polymorphisms in the *ITPKC* (inositol 1,4,5 triphosphate 3-kinase C) gene that are associated with increased risks of susceptibility to KD, more severe coronary artery disease, and lack of response to IVIG, termed *IVIG resistance*. (4) *ITPKC* acts as a negative regulator of T-cell activation through the calcineurin/NFAT signaling pathway, and alterations in signaling may contribute to immune hyperreactivity in KD. The *FCGR2A* locus has also been identified as a susceptibility locus by genome-wide association studies, and a recent study demonstrated that hypomethylation of this locus led to susceptibility to KD and to IVIG resistance.

To date, the role of B cells in the pathogenesis of KD has not been clearly elucidated. Immunoglobulin A plasma cells have been found in lung tissue and coronary arteries from fatal cases of KD, but the precise role of the immunoglobulin A plasma cells remains to be determined. Furthermore, a study using the murine model with *L casei* cell wall extract–induced coronary arteritis indicated that B cells are not required for the development of CALs.

CLINICAL ASPECTS

Classical clinical criteria with supportive clinical and laboratory findings are listed in Table 1. (5) Except for fever, the features of KD can fluctuate or accrue over time, and a thorough medical history is required to determine their presence during the course of illness. Children who have at least 4 days of fever and 4 or 5 of the principal criteria meet the case definition of KD. Very early diagnosis, ie, at day 3, can be conferred in rare cases where they child meets at least 4 of the principal criteria by day 3 of fever, or in the hands of an experienced KD clinician. The case definition also includes children with fewer than 4 criteria if they have coronary artery aneurysms.

The hallmark of KD is fever of abrupt onset, and it is typically greater than 102°F (>39°C) and may not remit with antipyretic medication use. In the absence of treatment, fever typically lasts 11 to 12 days, with rare cases of prolonged fever greater than 3 weeks. Although some children treated with IVIG experience immediate improvement during the infusion, others defervesce 1 to 2 days after IVIG therapy. Approximately 15% of children treated with IVIG have IVIG resistance or persistent or recrudescent fever more than 36 hours after completion of the first IVIG infusion.

More than 90% of children with KD develop bilateral nonexudative conjunctivitis that spares the limbus, ie, with clearing around the iris (Fig 2). In addition, anterior uveitis may be detected on slit lamp examination during the acute phase of the disease. Oropharyngeal manifestations are common and include a diffusely erythematous oropharynx, red cracked lips, and a strawberry tongue (Fig 3). Discrete oral ulcers and tonsillar exudates are not typically seen in KD.

The rash of KD usually appears within 5 days of fever and often starts as desquamation in the perineal area that then evolves into a diffuse, erythematous maculopapular rash. Morbilliform rashes, erythema multiforme, and erythroderma can also occur. Bullous or vesicular lesions suggest an alternative diagnosis. Reactivation at the site of bacille Calmette-Guérin vaccination has also been reported in KD.

Children with KD develop firm swelling of the hands and feet as well as erythema of the palms and soles in the acute phase of the disease. Characteristic, although not pathognomonic, periungual peeling from the fingers and the toes begins 2 to 3 weeks after onset of the fever (Fig 4). Peeling before day 10 of illness (ie, at the time of diagnosis) is not considered consistent with KD and may reflect desquamation seen in streptococcal or viral infections.

Cervical lymph node enlargement is the least common criterion found in patients with KD. It is usually unilateral, located in the anterior cervical chain, nonfluctuant, and nontender. The diameter of the involved node should equal or exceed 1.5 cm. Imaging typically reveals a group of matted nodes without abscess formation.

Children with KD can have a myriad of other symptoms, including myalgias, arthralgias, and arthritis. Neurologic involvement can include substantial irritability likely due to meningeal inflammation, transient facial palsies, and sensorineural hearing loss. Gastrointestinal complaints occur in up to 30% of patients, comprising abdominal pain, vomiting, diarrhea, acalculous distention of the gallbladder (hydrops), and hepatomegaly. Rarely, hemophagocytic lymphohistiocytosis, a potentially life-threatening complication in which activated macrophages and T cells cause a cytokine storm, can occur in KD.

Incomplete KD

A challenging subset of patients who do not meet the classic case definition are said to have incomplete or atypical KD. However, the term *atypical* should be avoided because children with incomplete KD do not have atypical features; rather, they have fever for five or more days and fewer than 4 of the classic features of KD and, thus, do not meet the case definition. Patients with incomplete KD are more likely to be infants and older children and, as such, are at higher risk for CALs. Considering the cardiac consequences of failing to treat incomplete KD and the comparative safety of IVIG treatment, the American Heart Association published an algorithm for the evaluation and treatment of suspected incomplete KD to assist clinicians (Fig 5). (5) The algorithm uses laboratory values and echocardiographic findings in children with only a few clinical features of the disease and also recommends consultation with a KD expert if needed. A multicenter retrospective study of patients with KD with aneurysms presenting before day 21 of illness found that application of the American Heart Association algorithm would have resulted in referral of 97% of patients for IVIG treatment. (6) Of note, infants younger than 6 months are at high risk for the development of CALs yet often have few clinical features to facilitate the diagnosis. For these reasons, it is recommended that infants younger than 6 month with fever for at least 7 days of unclear etiology and elevated inflammatory markers have an echocardiogram.

Differential Diagnosis

Because KD is a self-limited febrile illness, infections dominate the list of differential diagnoses (Table 2). Measles, adenovirus, enterovirus, and Epstein-Barr virus can mimic the clinical presentation of KD. Measles is not typically seen in countries with widespread vaccination; a travel or contact history should be sought in cases in which coryza and cough are conspicuous. Children with adenoviral or enteroviral illnesses are typically less ill compared with children with KD, and laboratory studies may show less evidence of inflammation with lower white blood cell counts and inflammatory markers. In addition, white blood cell indices typically reveal lymphocytosis. Epstein-Barr virus is commonly associated with an exudative pharyngitis and diffuse lymphadenopathy, neither of which is

TABLE 1. **Clinical and Laboratory Features of Kawasaki Disease (KD)**

Classic KD is diagnosed in the presence of fever for at least 5 d (the day of fever onset is taken to be the first day of fever) together with ≥4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 days of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 days of fever in rare cases.
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular diffuse erythroderma or erythema multiforme-like
4. Erythema and edema of hands and feet in the acute phase and/or periungual desquamation in the subacute phase
5. Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral
Other clinical and laboratory findings
• **Cardiovascular**
∘ Myocarditis, pericarditis, valvular regurgitation, shock
∘ Coronary artery abnormalities
∘ Aneurysms of medium-sized noncoronary arteries
∘ Aortic root enlargement
∘ Peripheral gangrene
• **Respiratory**
∘ Peribronchial and interstitial infiltrates on chest radiography
∘ Pulmonary nodules
• **Musculoskeletal system**
∘ Arthritis, arthralgia (pleocytosis of synovial fluid)
• **Gastrointestinal tract**
∘ Diarrhea, vomiting, abdominal pain
∘ Hepatitis, jaundice
∘ Hydrops of the gallbladder
∘ Pancreatitis
• **Central nervous system**
∘ Extreme irritability
∘ Aseptic meningitis
∘ Peripheral facial nerve palsy
∘ Sensorineural hearing loss
• **Genitourinary system**
∘ Urethritis/meatitis, hydrocele
• **Other findings**
∘ Desquamating rash in the groin
∘ Retropharyngeal phlegmon
∘ Erythema and induration at the bacille Calmette-Guérin site
∘ Anterior uveitis by slit lamp examination

Continued

TABLE 1. **(Continued)**

• Laboratory findings in acute KD
◦ Neutrophilia with immature forms
◦ Elevated erythrocyte sedimentation rate
◦ Elevated C-reactive protein level
◦ Elevated serum α1-antitrypsin level
◦ Anemia
◦ Abnormal plasma lipid levels
◦ Hypoalbuminemia
◦ Thrombocytosis after the first week of illness
◦ Sterile pyuria
◦ Elevated serum transaminase levels
◦ Pleocytosis of cerebrospinal fluid
◦ Leukocytosis in synovial fluid

Reprinted with permission from McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation. *2017;135(17):e927–e999.*

typically seen in KD. The conjunctivitis and rash of KD can be quite prominent and may appear consistent with Stevens-Johnson syndrome. The absence of other clinical features of KD or the presence of findings of skin pain, skin necrosis, or blisters favors the diagnosis of Stevens-Johnson syndrome. Toxin-mediated syndromes triggered by staphylococcal or streptococcal infections are usually characterized by visceral organ involvement, including renal insufficiency and substantial hepatic dysfunction, which are unusual in KD. Hypotension is also prominent in toxin-mediated illnesses. However, recent reports have documented a KD shock syndrome characterized by substantial hypotension in the acute phase of the disease requiring fluid resuscitation, vasoactive agents, and/or transfer to an ICU setting. Studies to date have been retrospective series but seem to indicate that KD shock syndrome is associated with worse coronary artery outcomes. Scarlet fever can be evaluated with rapid streptococcal antigen testing; fever caused by group A *Streptococcus* is not usually associated with conjunctivitis and usually improves significantly within 24 hours of initiation of antibiotic drug therapy. Rocky Mountain spotted fever presenting with fever and rash

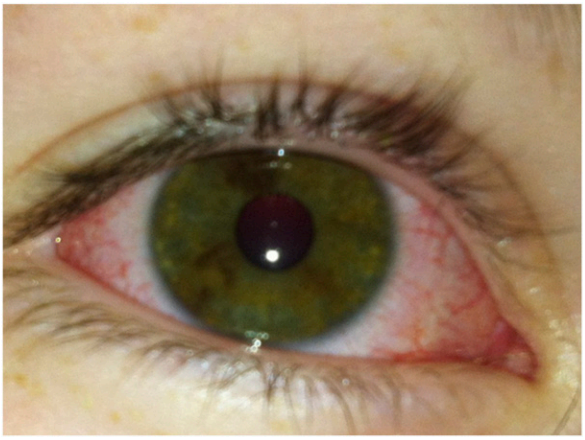

Figure 2. Bilateral nonexudative limbus-sparing conjunctivitis is found in greater than 90% of children with Kawasaki disease.

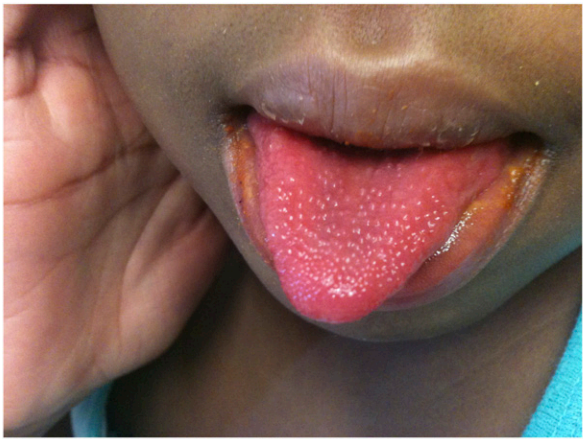

Figure 3. Oropharyngeal changes, including a strawberry tongue as pictured, are common in children with Kawasaki disease.

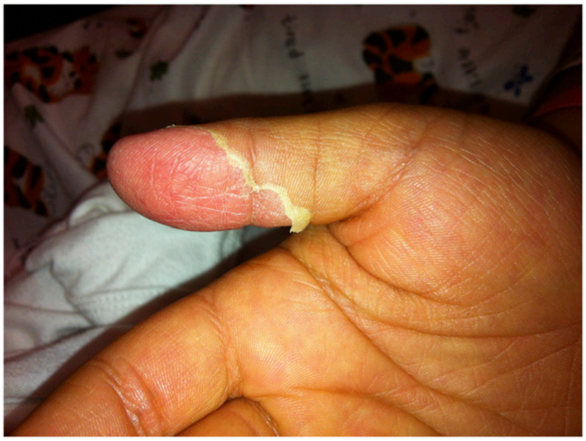

Figure 4. Periungual peeling, first from the finger nail beds and then the toes, is typically seen 2 to 3 weeks after onset of the fever.

can appear similar to KD and occurs in specific geographic regions in the United States; treatment for this potentially fatal infection should not be withheld while KD is being considered. Kawasaki disease presenting as "lymph node first" can mimic lymphadenitis of the cervical chain, but antibiotic drug therapy does not lead to defervescence, and other KD criteria may evolve with serial examinations. Acrodynia can cause irritability and extremity changes similar to KD; an ingestion history of mercury should be sought if these are prominent manifestations. Last, children with systemic-onset juvenile idiopathic arthritis present with fever and rash, and coronary dilatation on echocardiography has been described in this population. However, the ocular and oropharyngeal signs of KD are quite unusual in the systemic form of arthritis. Furthermore, children with systemic-onset juvenile idiopathic arthritis tend to have unremitting symptoms until more profound or more targeted immunosuppressive medications are used.

Concomitant infections do not preclude the diagnosis of KD. In a study from Toronto, more than 30% of children with typical KD had laboratory evidence of at least 1 infection. (7) Patients with KD have nonspecific symptoms as well, such as headache, abdominal pain, and malaise. Clinicians should not dismiss the diagnosis of KD in children with symptoms that are commonly attributed to viral illnesses.

EVALUATION OF A PATIENT WITH SUSPECTED KD

Laboratory Studies

Children with KD typically have leukocytosis with a predominance of neutrophils and immature forms. Many

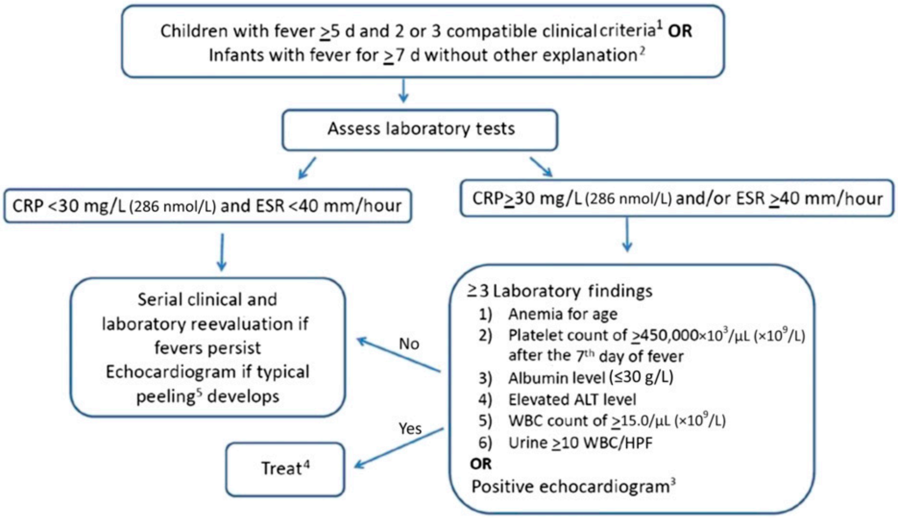
Children with fever ≥5 d and 2 or 3 compatible clinical criteria^{1} OR
Infants with fever for ≥7 d without other explanation^{2}
Assess laboratory tests
CRP <30 mg/L (286 nmol/L) and ESR <40 mm/hour
CRP≥30 mg/L (286 nmol/L) and/or ESR ≥40 mm/hour
Serial clinical and laboratory reevaluation if fevers persist
Echocardiogram if typical peeling^{5} develops
No
Yes
Treat^{4}
≥3 Laboratory findings
1) Anemia for age
2) Platelet count of ≥450,000×10^{3}/μL (×10^{9}/L) after the 7th day of fever
3) Albumin level (≤30 g/L)
4) Elevated ALT level
5) WBC count of ≥15.0/μL (×10^{9}/L)
6) Urine ≥10 WBC/HPF
OR
Positive echocardiogram^{3}

Figure 5. Evaluation of suspected incomplete Kawasaki disease (KD). In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. 1) Clinical findings of KD are listed in Table 1. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, or splenomegaly. 2) Infants 6 months or younger are the most likely to develop prolonged fever without other clinical criteria for KD; these infants are at particularly high risk for coronary artery abnormalities. 3) Echocardiography is considered positive for the purposes of this algorithm if any of 3 conditions are met: the *Z* score of the left anterior descending coronary artery or right coronary artery is at least 2.5, coronary artery aneurysm is observed, or 3 or more other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or *Z* scores in the left anterior descending coronary artery or right coronary artery of 2 to 2.5. 4) If the echocardiographic result is positive, treatment should be given within 10 days of fever onset or after the 10th day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. 5) Typical peeling begins under the nail beds of the fingers and toes. ALT=alanine aminotransferase; HPF=high-power field; WBC=white blood cell. (Reprinted with permission from McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation.* 2017;135(17):ee937.)

TABLE 2. **Differential Diagnosis of Kawasaki Disease**

Infections
• Viral
◦ Measles
◦ Adenovirus
◦ Enterovirus
◦ Epstein-Barr virus
• Bacterial
◦ Scarlet fever
◦ Cervical lymphadenitis
◦ Rocky mountain spotted fever
◦ Leptospirosis
Toxin-mediated diseases
• Staphylococcal scalded skin syndrome
• Toxic shock syndrome (associated with *Staphylococcus* or *Streptococcus*)
Hypersensitivity reactions
• Drug hypersensitivity reactions
• Stevens-Johnson syndrome
Other
• Systemic-onset juvenile idiopathic arthritis
• Acrodynia (mercury toxicity)

children have a normocytic normochromic anemia, with the average hematocrit level at presentation being 2 standard deviations below the norm for age. A sudden drop in hemoglobin concentration after IVIG therapy may be due to hemolytic anemia. Platelet counts are usually elevated by the end of the first week of illness ($450{,}000/\times10^3/\mu L$ ($\times10^9/L$)) and may evolve into major thrombocytosis, with platelet counts averaging $700{,}000/\times10^3/\mu L$ ($\times10^9/L$) by the third week. Platelet counts exceeding 1 million/$\times10^3/\mu L$ ($\times10^9/L$) are not uncommon. Relatively lower platelet counts at the time of presentation are a risk factor for later development of CALs, likely reflecting greater adherence of platelets to an activated endothelium. Rarely, marked thrombocytopenia at diagnosis may be due to diffuse intravascular coagulation.

Inflammatory markers are elevated in nearly all patients with KD. The erythrocyte sedimentation rate (ESR) and CRP should be assessed at the time of diagnosis. The ESR after treatment with IVIG is often high as the protein load elevates the ESR and obscures the extent of disease activity; therefore, rechecking the ESR after treatment is not informative. Nonetheless, measurements of the ESR can be helpful in assessing the degree of inflammation at diagnosis. Levels of CRP are unaffected by IVIG and can be used in the acute and subacute phases to gauge the degree of inflammation.

Transaminase levels are elevated in approximately 40% of patients with KD, and a mild hyperbilirubinemia can occur. Plasma γ-glutamyl transpeptidase levels are elevated in approximately two-thirds of patients with KD. Sterile pyuria (ie, culture negative) with a white blood cell count of at least $12/\mu L$ ($\geq 0.01\times10^9/L$) is present in approximately 80% of patients with KD. Such pyuria may also be found in children with other febrile illnesses, but the magnitude is greater in patients with KD. Laboratory findings such as hypoalbuminemia and hyponatremia reflect more severe illness and can be associated with capillary leak. Lipid panels in patients with KD are markedly altered, with decreased levels of total cholesterol as well as apolipoprotein A1 and high-density lipoprotein. Markers of cardiac damage or dysfunction, such as troponins and B-type natriuretic peptide, may also be elevated but are not routinely obtained.

Although laboratory studies are not a component of the classical criteria for KD, they are included in the algorithm for treatment of suspected incomplete KD because many of the laboratory abnormalities described previously herein are seen consistently in KD.

The child has an echocardiogram performed. Her coronary artery dimensions are within normal limits for age, but her left anterior descending artery (LAD) does not taper normally. Her left ventricular function is normal, and no pericardial effusion is seen.

Cardiac Imaging

Echocardiography is an excellent imaging modality to evaluate coronary artery dimensions in infants and children. In addition, this imaging modality provides evaluation of myocardial function, valve regurgitation, and pericardial effusion. It is noninvasive and in experienced hands has high sensitivity and specificity for dilatation in the proximal coronary arteries. Sedation is often required in younger children to obtain optimal images. If the diagnosis is clear, treatment for KD should not be withheld while waiting to schedule or obtain the results of an echocardiogram. Two-dimensional echocardiograms should be performed with the highest frequency probe available to produce high-resolution images. Standard views for cardiac echocardiography include parasternal, apical, subcostal, and suprasternal notch windows. Patients with definite or suspected KD should undergo assessment of each coronary artery, including the left main coronary artery, LAD, left circumflex coronary artery, right coronary artery (RCA), and posterior descending coronary artery. The proximal LAD and RCA are most commonly affected by coronary artery aneurysms.

Coronary arteries should be evaluated with respect to their size and appearance. The size of an artery should be measured from internal edge to internal edge, avoiding areas of branching that can be associated with areas of natural dilatation. The widely used Japanese Ministry of Health criteria classify coronary artery sizes according to age, with an internal lumen diameter greater than 3 mm abnormal in children younger than 5 years and an internal lumen diameter greater than 4 mm abnormal in children 5 years or older. In addition, artery segments that are 1.5 times or more larger than the adjacent section and segments with an irregular coronary lumen are also considered abnormal. As coronary artery dimensions change with the size of the child, body surface area–adjusted coronary dimensions (*z* scores) should also be obtained for the left main coronary artery, LAD, and RCA. The other coronary arteries do not have established *z* scores, and, as such, the Japanese Ministry of Health criteria may be applied to those segments. Aneurysms can be classified as small (<5-mm internal diameter), medium (5–8-mm internal diameter), and large (>8-mm internal diameter) when using absolute dimensions.

The appearance of the coronary arteries is also informative. In most children with KD, coronary diameters are greatest at the first echocardiogram performed early in the disease. (8) Larger baseline measurements predict the development of worsening CALs over the ensuing 4 to 6 weeks in a subset of children. If coronary artery dimensions are normal in the subacute period (up to 6 weeks), it is highly unlikely that the child will develop dilatation of coronary vessels thereafter unless the disease relapses or recurs.

In addition to documenting findings in the coronary arteries, echocardiography provides assessment of left ventricular and valve function. Left ventricular systolic dysfunction, ie, an ejection fraction more than 2 standard deviations below normal, occurs in 20% of children with acute KD. Histologic studies suggest that myocarditis is universal in patients with KD and can be severe enough to produce a clinical picture consistent with shock. The myocarditis rapidly improves with administration of IVIG. The pericardium should be assessed with echocardiography for evidence of effusion. Last, although mitral regurgitation is seen in 27% of patients early in the course of KD, aortic regurgitation is less common (1%).

Echocardiography should be performed at diagnosis, 1 to 2 weeks later, and 5 to 6 weeks after hospital discharge. Importantly, children with persistent or recrudescent fever or with coronary artery dilatation (even mild dilatation at baseline echocardiography) need more frequent monitoring to inform treatment decisions, and close follow-up with a pediatric cardiologist is essential. The frequency of echocardiography in children with CALs should be tailored to the degree of enlargement in the coronary artery, the stability of coronary dimensions (ie, more frequent echoes should be performed when coronary dimensions are enlarging), and the patient's severity of inflammation. Children with giant coronary aneurysms in the acute and subacute phases of illness benefit from frequent (eg, twice weekly) echocardiographic surveillance for thrombus formation. Thrombi that occlude or nearly occlude the vessel lumen require thrombolytic therapy, ideally in the hands of experts in cardiology, hematology, and intensive care.

Although echocardiography is the preferred method of visualizing the coronary arteries early after KD, more comprehensive imaging of coronary arteries in children with significant coronary artery aneurysms is obtained using techniques of computed tomographic angiography, magnetic resonance angiography, or cardiac catheterization.

Based on the clinical findings, the child is diagnosed as having KD and is prescribed IVIG (2 g/kg) and aspirin (ASA) (30–50 mg/kg per day divided every 6 hours).

MANAGEMENT

Once the diagnosis of KD is confirmed, treatment with high-dose IVIG (2 g/kg) and ASA should be instituted promptly.

Ideally, treatment is administered within the first 7 days of illness and by day 10 (as defined by the first day of fever) at the latest. Treatment with IVIG after day 10 of illness is reserved for those with ongoing fever, or those with evidence of systemic inflammation on laboratory studies and coronary artery abnormalities. To avoid infusion reactions, premedication with standard dosing of diphenhydramine or another antihistamine should be strongly considered. In addition, IVIG should be administered slowly, over 8 to 12 hours, to avoid hemodynamic instability. Use of IVIG can be associated with low-grade fevers within the first 48 hours of its administration. Hemolytic reactions to IVIG are well described and have become more frequent in recent years, although the reason for the rise in incidence is unclear. The risk of hemolysis is typically dose dependent (ie, patients who received >1 dose of IVIG are at higher risk). Children with non-O blood types are at risk for hemolysis. Approximately 15% of children with KD will have recurrent or persistent fever after the first dose of IVIG and are at higher risk for CALs. The treatment of these children remains an area of controversy because studies to evaluate treatment strategies for IVIG resistance are limited. Most clinicians administer another dose of IVIG (2 g/kg) 48 hours after the first dose if fever persists or is recrudescent.

Because KD is a vasculitis, there have been trials of corticosteroid therapy in KD. Corticosteroids can be administered as primary therapy when given at the time of the first dose of IVIG or as secondary therapy when given for IVIG resistance. Furthermore, they can be given in high pulse doses of 30 mg/kg of intravenous methylprednisolone or in lower doses (0.5–2 mg/kg per day) of prednisolone orally. The use of corticosteroids in KD has an interesting history, as an early report raised the possibility of corticosteroids worsening coronary artery disease. However, subsequent studies indicated a likely beneficial effect in children. The RAISE trial (Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy in Kawasaki Disease) by Kobayashi et al (9) involving high-risk Japanese children showed that primary therapy with a combination of corticosteroids (prednisolone [2 mg/kg per day]) and IVIG provided protection against poor coronary outcomes. This study met the primary end point of reduction in coronary artery abnormalities, and all secondary end points, including *z* scores of coronary arteries, duration of fever after enrollment, and need for additional rescue treatment. However, this regimen has not been formally tested in non-Japanese populations, and it involved a prolonged course of intravenous corticosteroids with concomitant hospitalization. The optimal regimen of corticosteroids for IVIG resistance has yet to be determined, and the lack of consensus has fostered considerable practice variation across centers.

Other therapies used in KD include infliximab, a tumor necrosis factor inhibitor (5 mg/kg per dose). Retrospective data indicated that infliximab might decrease the number of days of fever but not alter coronary artery outcomes. Similarly, results of a prospective trial using infliximab as primary therapy did not demonstrate a decrease in CALs at the end of the study period. (10) Last, there are reports from Japan (11) and the United States that calcineurin inhibitors such as cyclosporine may be effective in patients with IVIG resistance; the results of a prospective Japanese trial are awaited.

There are very few indications for ASA in childhood given the risk of Reye syndrome, but KD remains one of them. Studies have shown that the use of ASA does not impact the development of CALs. However, all of the major clinical trials to study treatment of KD have used ASA. Use of other nonsteroidal anti-inflammatory drugs, such as ibuprofen, has not been recently studied. In KD, ASA is given at medium (30–50 mg/kg per day) to high (80–100 mg/kg per day) divided doses every 6 hours initially, followed by antithrombotic doses of 3 to 5 mg/kg per day in once-daily dosing. Because ASA does not change coronary artery outcomes, it is reasonable to give medium-range doses of ASA and avoid the potential toxicity of high-dose ASA.

There is practice variation in the duration of high-dose ASA administration. Some practitioners give higher doses of ASA until patients are afebrile for 48 hours, and others continue with high-dose ASA for 2 weeks. Low-dose ASA treatment is typically discontinued if the echocardiographic findings are normal at the 6-week visit. Children with persistent CALs at 6 weeks continue taking low-dose ASA, and yearly influenza vaccinations are strongly recommended in those cases to decrease the risk of Reye syndrome. Patients receiving long-term ASA who are not fully vaccinated should receive immunizations according to the guidelines put forth in the American Academy of Pediatrics' Red Book, which state that measles and varicella-containing vaccinations are contraindicated for 11 months after administration of IVIG for KD. For patients with moderate to large aneurysms, a second antiplatelet agent may be added to ASA. Children with giant aneurysms require anticoagulation with low-molecular-weight heparin or warfarin in addition to ASA. Such regimens are best implemented with the collaboration of pediatric hematologists or coagulation services.

The role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in children with KD remains an area of research. Statins have both cholesterol-lowering and immunomodulatory properties. In a small study of 11 children with KD and CALs, use of a statin for 3 months resulted in improved flow-mediated dilation (an indication of endothelial health) and CRP levels. Although these results are of interest, larger-scale clinical trials are needed before one can recommend use of statins in the earliest phases of KD. However, the threshold for use of statins in children with aneurysms is lower because of data suggesting their susceptibility to atherosclerosis.

The patient tolerates her IVIG infusion without complication and defervesces within the subsequent 48 hours. Her tachycardia resolves. On examination, the conjunctival injection significantly improves, as does the rash. On discharge, she is well appearing and prescribed half a baby ASA (40.5 mg) daily. She is scheduled for an appointment with the cardiology department in 1 to 2 weeks for echocardiography and laboratory studies.

PROGNOSIS AND LONG-TERM MANAGEMENT

The prognosis of KD relates entirely to the extent and severity of cardiac disease. With timely IVIG treatment, the incidence of CALs in treated children has fallen to less than 5%, and only 1% of children develop giant aneurysms. Coronary aneurysms regress to normal lumen diameter via proliferation of myofibroblasts in more than half of the affected arterial segments. However, endothelial function is impaired in these segments even after regression. Stenoses at the proximal and distal ends of aneurysms can develop over time and increase the risk of myocardial ischemia. Stenotic lesions are more likely to form in giant aneurysms compared with smaller lesions.

Management of children with major coronary artery disease may require a combination of β-blockers to decrease oxidative stress and antithrombotic therapy. These children are followed closely with assessment of coronary function (eg, exercise stress echocardiography in children old enough to run on a treadmill and dobutamine stress cardiac MRI for younger children) and structure (eg, echocardiography, coronary angiography by CT, MRI, or cardiac catheterization). In those who develop symptoms of angina or findings of reversible ischemia on stress testing, percutaneous coronary intervention, for example with coronary stents, or coronary artery bypass surgery may be indicated. A report from Japan that followed patients with giant aneurysms into adulthood found that long-term survival is relatively good in patients with giant aneurysms despite their need for multiple catheterizations and surgeries. (12)

Mortality from KD is low (<0.5%), with the highest risk occurring in the first year after illness onset due to acute myocardial infarction in patients with giant aneurysms. Sluggish blood flow through a dilated arterial segment and activation of platelets and endothelium contribute to the risk of myocardial infarction. Children with myocardial infarction may present with pallor, vomiting, and abdominal pain; older children may complain of chest pain. Rupture of coronary artery aneurysms is rare and generally occurs within the first few months of illness. Severe myocarditis leading to hemodynamic compromise and/or arrhythmias can lead to death in the first week of illness.

Fortunately, most children with KD do well after receiving a single dose of IVIG, with rapid clinical improvement and reassuring echocardiographic findings. A study of Californian adults who had developed KD as children (average age at time of analysis was 21 years) revealed a low rate of cardiovascular complications. (13)

The risk of premature atherosclerosis in patients with always-normal coronary arteries will not be known definitively until large cohorts of middle-aged patients with KD are assembled. In the interim, all children with a history of KD, even those without apparent coronary artery involvement, should undergo assessment of risk factors, such as hyperlipidemia and hypertension, and should be counseled regarding a healthy lifestyle and avoidance of modifiable cardiac risk factors, such as obesity, smoking, and a sedentary lifestyle.

Summary

- Patients with acute Kawasaki disease (KD) should be treated promptly with intravenous immunoglobulin (IVIG) to prevent coronary artery abnormalities (based on strong research evidence). (14)
- Patients who have persistent or recrudescent fever after primary therapy with IVIG should receive additional immunomodulatory therapy. The most common practice is administration of a second dose of IVIG at 2 g/kg (based primarily on expert consensus). (15) Other secondary therapies to consider include corticosteroids (16)(17) and infliximab (18) (based on some research evidence).
- Echocardiography is an excellent modality for assessing proximal coronary artery changes in infants and young children with early KD.
- In patients with KD and always-normal coronary arteries, preventive cardiology counseling and follow-up is recommended until further studies delineate the long-term consequences on endothelial health (based on limited research evidence as well as consensus). (15)
- In patients with KD and coronary aneurysms, cardiologic follow-up is tailored to the degree of coronary artery involvement and involves serial assessment of coronary function and structure (based on strong research evidence). (15)

References for this article are at http://pedsinreview.aappublications.org/content/39/2/78.

PIR Quiz

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1. A 3-year-old Korean boy in your practice was evaluated in the emergency department over the weekend for 5 days of fever, rash, and conjunctivitis. He was admitted to the hospital with the diagnosis of Kawasaki disease (KD). Physical examination on admission was consistent with findings of KD, including fever, a polymorphous nonpruritic rash, conjunctivitis, and mucosal findings. Laboratory studies on admission showed a complete blood cell count with a white blood cell count of 18,000/μL (18×10^9/L) (80% neutrophils) and a platelet count of $600\times10^3/\mu$L (600×10^9/L). A complete metabolic panel was significant for a sodium level of 129 mEq/L (129 mmol/L) and mildly elevated liver enzyme levels. His C-reactive protein level was 88 mg/L (838 nmol/L), and his erythrocyte sedimentation rate was 68 mm/hour. Results of a rapid strep test were negative. A throat culture is pending. He was started on intravenous immunoglobulin (IVIG) per protocol. The parents are concerned about the prognosis and the response to treatment. In assessing his prognostic factors, which of the following factors does not place him at higher risk for a poor outcome?
   A. Age.
   B. Elevated C-reactive protein level.
   C. Sex.
   D. Hyponatremia.
   E. Race.
2. A 5-year-old girl presents to the clinic with 7 days of fever that responds occasionally to acetaminophen. Her physical examination is significant for an erythematous tongue, bilateral conjunctival injection, a maculopapular rash, and cervical lymphadenopathy. She is diagnosed as having KD. Which of the following clinical findings on examination of her hands and feet is most likely to be seen during the acute phase of the disease in this patient?
   A. Bruising of the fingers and toes.
   B. Desquamation of the fingers and toes.
   C. Firm swelling of the palms and soles.
   D. Hemarthrosis of the ankles and wrists.
   E. Lytic lesions in the long bones of the upper and lower extremities.
3. The patient in question 2 is admitted to the hospital for evaluation and management. In determining whether this patient will need to have further infectious evaluation for bacteria and viruses, which of the following represents the percentage of children with KD who might have a coexisting infection?
   A. 10%.
   B. 30%.
   C. 50%.
   D. 70%.
   E. 80%.
4. A 4-year-old Pacific Islander boy is diagnosed as having KD on day 6 of illness. He is admitted to the hospital for further management. Laboratory studies are obtained, and an intravenous peripheral line is placed. Which of the following is the most appropriate initial treatment regimen?
   A. Aspirin (40 mg/kg per day) plus IVIG (2 g/kg per day).
   B. Aspirin (100 mg/kg per day) plus solumedrol (30 mg/kg per day).
   C. Aspirin (80 mg/kg per day) plus solumedrol (2 mg/kg per day).
   D. IVIG (2 g/kg per day) plus cyclosporine (9 mg/kg per day).
   E. IVIG (2 g/kg per day) plus infliximab (5 mg/kg per dose).

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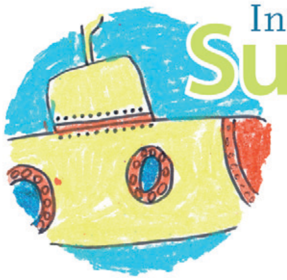
5. A 6-year-old girl is diagnosed as having KD on day 6 of illness and is treated with IVIG (2 g/kg) and aspirin (50 mg/kg per day). She is up to date on her immunizations. Follow-up echocardiography at 6 weeks shows persistent coronary artery lesions, and low-dose aspirin therapy is continued. She comes to her pediatrician for her yearly health supervision visit before starting school in the fall. Which of the following vaccines is recommended during this visit for this patient?
   - A. Measles.
   - B. Varicella.
   - C. Influenza.
   - D. Tetanus.
   - E. No vaccines are recommended at this point.



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1 Vomiting and Ventricular Arrhythmia in a 2-year-old Girl

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Kathryn W. Holmes, MD, MPH,* Judith A. Guzman-Cottrill, DO*

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Gern, Mehta, McCammond, Holmes, and Guzman-Cottrill have disclosed no financial relationships relevant to this article. Dr Gern's current affiliation is Department of Pediatrics, University of Washington, Seattle, WA. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year-old girl presents to an urgent care clinic with a 1-day history of nonbloody, nonbilious vomiting, intolerance of oral intake, and decreased urine output. There is no present history of fever, abdominal pain, diarrhea, cough, trauma, or travel. Two weeks before presentation, she recovered from a febrile illness. In urgent care, she is treated with two 20-mL/kg normal saline boluses and intravenous ondansetron and is admitted to the general ward for monitoring and intravenous fluid rehydration.

On hospital admission she is afebrile, and vital signs include a heart rate of 106 beat/min and elevated blood pressure of 121/69 mm Hg. She is sleeping but awakens appropriately with examination. The rest of her physical examination findings are normal.

Her complete blood cell count shows a white blood cell count of 18,800/μL ($\times 10^9$/L), with 85.1% neutrophils; a hemoglobin level of 10.5 g/dL (105 g/L); and a platelet count of 451×10^3/μL (451×10^9/L). A comprehensive metabolic panel is notable for an aspartate aminotransferase level of 104 U/L (1.74 μkat/L) (reference range, 5–43 U/L [0.08–0.72 μkat/L]) but is otherwise normal (including normal electrolyte levels).

Four hours later, the patient is found pulseless and apneic. There is brief return of spontaneous circulation with cardiopulmonary resuscitation and epinephrine and sodium bicarbonate administration. Continuous electrocardiogram monitoring demonstrates ventricular tachycardia (VT) with deterioration to ventricular fibrillation (VF) (Fig). She continues to have multiple cardiac arrests with VT/VF requiring defibrillation, cardiopulmonary resuscitation, and, eventually,

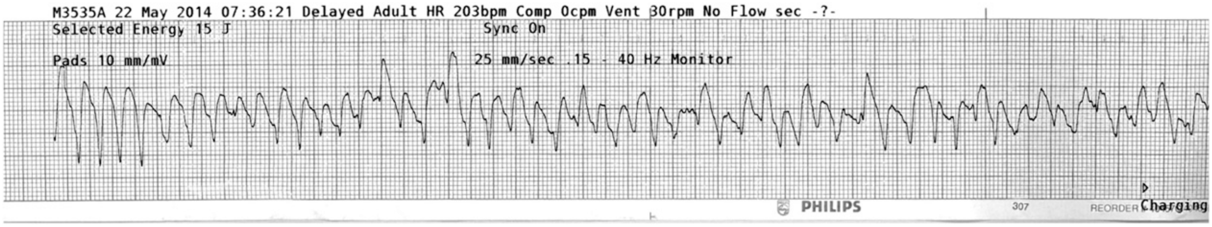
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Figure. Continuous electrocardiogram monitoring showing ventricular tachycardia and fibrillation.

cannulation to veno-arterial extracorporeal membrane oxygenation. Cardiac imaging reveals the cause of her acute event.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/2/91.

DISCUSSION

Transthoracic echocardiogram revealed a normal-sized heart, moderate to severely depressed global biventricular function, and normal-appearing left ventricular size and thickness. There was no pericardial effusion. Notably, there was severe dilation of the left anterior descending coronary artery (5.9 mm, z+16) and right coronary artery (4.2 mm, z+7.2), with mild dilation of the left main coronary artery (3.2 mm, z+2.4). No blood flow was visualized in the distal coronary arteries.

On further questioning, it was discovered that 2 weeks before admission she was evaluated by her pediatrician on the fourth day of fever during that 11-day febrile episode. Her pediatrician documented mild bilateral conjunctival injection and oropharyngeal erythema. At that time, a urine sample demonstrated sterile pyuria. Based on this history she was diagnosed as having incomplete Kawasaki disease (KD) and subsequent coronary aneurysms, leading to myocardial ischemia and cardiovascular collapse.

The Condition

First described by Dr Tomisaku Kawasaki in 1967, KD is a well-described systemic vasculitis and the most common cause of acquired pediatric heart disease in the developed world. Clinical features include a temperature of 100.4°F or higher (≥38.0°C), bilateral nonpurulent conjunctivitis, oral mucosal inflammation, polymorphous rash, extremity changes of the hands and feet, and cervical adenopathy. The acute febrile phase generally lasts 10 to 12 days and is self-limited. If untreated during the acute phase, KD can lead to cardiac complications in 15% to 25% of affected individuals. Complications may include coronary artery aneurysms (CAAs) and potentially fatal coronary insufficiency, myocardial ischemia, and infarction.

The formation of CAAs in KD is a direct result of the inflammatory process. On days 7 to 9 of illness, there is a neutrophil infiltration into the coronary artery walls that is quickly replaced by monocytes, lymphocytes, and IgA plasma cells. This response causes fragmentation of the elastic lamina and damage to the media, resulting in aneurysm formation. As the acute inflammation recedes, these areas of remodeling can undergo fibrosis and scar formation. Risk factors that increase a patient's risk of developing CAA include delay of intravenous immunoglobulin (IVIG) administration past the 10th day of illness, persistent fever after IVIG administration, elevated inflammatory markers, a white blood cell count more than 12,000/μL (12×10^9/L), anemia, hyponatremia, thrombocytopenia, hypoalbuminemia, male sex, and younger than 12 months.

Differential Diagnosis

This patient's initial presentation was thought to be consistent with acute viral gastroenteritis. Rarely, viral gastroenteritis can proceed to cardiovascular collapse in the setting of extreme volume depletion, potassium disturbances, or acid/base disturbances, none of which were present in this patient. Before the echocardiogram, viral myocarditis and underlying cardiomyopathy were high on the differential diagnosis. The presentation of recalcitrant VT/VF is extremely rare in children and broadened the differential diagnosis to include congenital abnormalities of myocardial conduction, such as Brugada syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. The recurrence of ventricular arrhythmias in an otherwise healthy child can also suggest myocardial ischemia and coronary insufficiency. The additional history of an 11-day febrile illness with 2 of 5 associated clinical criteria of KD and supplemental laboratory findings (white blood cell count, anemia, sterile pyuria, aspartate aminotransferase level elevation) were instrumental in increasing the suspicion of KD.

Management

In 2004, the American Heart Association published guidelines for the management of KD. Treatment in the acute phase includes high-dose IVIG (2 g/kg) and high-dose oral aspirin (80–100 mg/kg per day). Ideally, treatment should be administered within the first 10 days of fever.

No data exist from randomized controlled trials to aid in directing treatment when coronary manifestations are observed on initial presentation. When coronary aneurysms are present, IVIG and aspirin are still administered. Dipyramidole or clopidigrel are often added for increased antiplatelet effect. When giant or rapidly expanding coronary aneurysms are present, warfarin and/or heparin therapy may also be considered. The American Heart Association KD guidelines state that the usefulness of corticosteroids in initial treatment is not well established. (1) However, corticosteroids are often used for patients who are refractory to IVIG plus oral aspirin. A retrospective Japanese study demonstrated that children who received IVIG plus prednisolone for first-line IVIG nonresponders had a lower risk of failing to respond compared with the IVIG group. (5)

Once the patient develops coronary thrombus or evidence of cardiac ischemia, the previously described treatment may provide some benefit, but more invasive procedures must be considered. Percutaneous transluminal coronary balloon angioplasty can be used to relieve mild to moderate stenosis, although there is a relatively high rate of restenosis (25%).

Other more advanced interventions, such as stent placement, percutaneous transluminal coronary rotational ablation, and percutaneous transluminal coronary revascularization, have shown promising results in small sample sizes, although these techniques are frequently limited by patient size.

Our patient was treated with IVIG and methylprednisolone owing to the severity of her clinical presentation and coronary artery disease. In addition, she was anticoagulated with heparin while undergoing veno-arterial extracorporeal membrane oxygenation. However, she died of complications related to anticoagulation.

Lessons for the Clinician

- Consider Kawasaki disease in febrile children with any manifestations of Kawasaki disease, including children with only 1 or 2 clinical features.
- Consider acute cardiac disease or myocardial ischemia in patients with recalcitrant ventricular arrhythmias who do not improve with the pediatric advanced life support algorithm.
- Kawasaki disease should be highly considered in pediatric patients with acute cardiac disease/myocardial infarction.
- Kawasaki disease should be considered as a cause of ventricular fibrillation, especially in young children, where it is especially rare.

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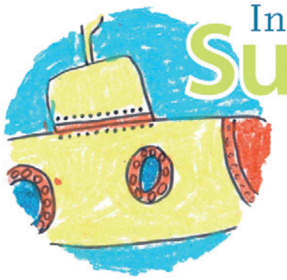

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Headache and Behavior Changes in an 11-year-old Boy

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AUTHOR DISCLOSURE Drs Mills, Yock, and King have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 11-year-old previously healthy boy presents with 2 days of eye pain, headache, slowed speech, and word-finding difficulty. One day before presentation he attended school and football practice without any noted behavior change, trauma, confusion, or coordination difficulty. On the day of presentation, he awoke with left-sided headache and decreased appetite. He appeared "dazed" and unable to answer basic questions and was brought to the emergency department. He had no fevers or recent illness. He had exposure to outside farm cats, mosquitoes, and stream water, but no exposure to lakes or swimming pools. He has no known history of tick exposure or ill contacts.

On physical examination, the patient is afebrile (99.7°F [37.6°C]) and appears uncomfortable. His heart rate is 80 beats/min; respiratory rate, 18 breaths/min; blood pressure, 108/55 mm Hg; and oxygen saturation, 98% in room air. When asked what time it is, he responds by asking an unrelated question ("How tall is it?"). His speech pattern is normal. There are no cranial nerve deficits or clonus observed. Slight pain is elicited with forward neck flexion. His balance and gait are intact, and his strength is equal bilaterally. Sharp optic disc margins are noted. Cardiorespiratory examination findings are normal, and no heart murmur is appreciated. Oral examination findings are normal. No cutaneous lesions are noted. He is hospitalized for further evaluation of acute mental status change and left temporal headache. Additional history and imaging studies help establish the diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/2/93.

DISCUSSION

Admission laboratory evaluation revealed a normal complete blood cell count and complete metabolic panel and normal levels of C-reactive protein, ammonia, and lactate. Findings from a drug screen and head computed tomographic scan were normal. A cerebrospinal fluid analysis revealed clear fluid with 6 white blood cells and unremarkable protein and glucose levels. An array of infectious disease tests were ordered on cerebrospinal fluid and serum.

On the second full hospital day the patient developed a fever (102.7°F [39.3°C]), worsening headache, and vomiting. Additional history was obtained revealing a recent dental abscess and tooth extraction 2 weeks before the onset of symptoms. He did not require prophylactic antibiotics before the procedure given his unremarkable medical history. Brain magnetic resonance imaging revealed multiple tiny foci of cortical and medullary enhancement of the bilateral cerebral hemispheres. An echocardiogram revealed a small mobile attachment on the left ventricular surface of the aortic valve with aortic regurgitation consistent with vegetation. The echocardiogram otherwise showed normal cardiac anatomy. The patient was diagnosed as having septic embolic encephalitis secondary to infectious endocarditis (IE).

The patient was subsequently transferred to the PICU due to progressive encephalopathy, difficulty waking, and the need for close neurologic monitoring. All laboratory results were normal except for a LaCrosse encephalitis immunoglobulin (Ig) G (IgM negative), which was attributed to a past exposure. Serial blood cultures were negative. Metronidazole was added for additional oral flora coverage given the history of dental procedure and blood culture obtained after initiation of antibiotic therapy. By the ninth hospital day, the patient's cognition had returned to near normal. A peripherally inserted central catheter was placed, and the patient was discharged from the hospital on an extended course of meropenem for presumed culture-negative endocarditis. Follow-up echocardiography 6 weeks after hospitalization demonstrated resolution of aortic regurgitation and vegetation. The cause of IE in our patient was consistent with bacterial seeding after a dental procedure involving gingival manipulation given his otherwise unremarkable medical history and normal cardiac anatomy.

The Condition

Infectious endocarditis, defined as an infection of the endocardium most commonly from a bacterial or fungal source, is a rare condition in children. Most IE cases occur in patients with known repaired or unrepaired congenital heart disease (CHD), and IE in structurally normal hearts accounts for 5% to 13% of cases. Other risk factors for IE include history of rheumatic heart disease, prosthetic valves, history of endocarditis, and hospital device–associated bacteremia. In patients with structurally normal hearts, a history of prematurity and a central indwelling catheter have been found to increase the risk of developing IE. Bacteremia secondary to dental instrumentation is thought to be a rare cause of IE in children. The most common pathogens of IE in both patients with CHD and structurally normal hearts are *Staphylococcus aureus and Streptococcus viridans,* yet a variety of gram-negative bacteria account for the remaining cases of bacterial IE. In approximately 5% to 10% of patients with IE the bacterial cultures are negative.

Morbidity and mortality due to secondary complications such as mycotic aneurysm, abscess formation, and septic emboli may affect up to 30% of patients with IE. Septic embolic encephalitis is characterized by an acute, fluctuating delusional state. Other neurologic complications include cerebral artery occlusion resulting in ischemia or hemorrhage, infection of the cerebral parenchyma or meninges resulting in microabscesses, and arterial wall infection, which may lead to mycotic aneurysm and subsequent hemorrhage. Clinical symptoms vary widely and depend on the location, size, and number of septic emboli. Patients with end-organ dysfunction such as neurologic involvement may require close ICU monitoring.

Differential Diagnosis

The initial differential diagnosis in children presenting with altered mental status include viral and bacterial encephalitis, postinfectious encephalitis (ie, acute disseminated encephalomyelitis), autoimmune encephalopathy, or atypical migraine headache. Other etiologies, including trauma, tumor, ingestion, seizure, and vascular events, should be considered. In our patient, initial evaluation was most concerning for a viral infectious etiology, yet his turbulent illness course, development of fever, and positive history of aortic valve vegetation in the setting of a recent dental procedure raised red flags for a septic embolic event secondary to IE.

Management

Treatment of IE involves the management of acute secondary complications, prompt initiation of empirical antibiotics, and possible surgical intervention. Prompt initiation of antibiotic therapy significantly reduces the risk of further endocardial damage and subsequent thromboembolic events. Empirical antibiotic therapy involves coverage of *S aureus* and *S viridans*, with subsequent tailoring to blood culture speciation. It is recommended that 3 or more blood cultures be obtained to aid in pathogen identification. Antibiotic courses are typically 4 to 6 weeks. Surgical intervention may be indicated for removal of vegetation or replacement of damaged cardiac valves. Given the complex nature of IE, a multidisciplinary approach is recommended, including consultation with infectious disease, cardiology, cardiovascular surgery, and/or neurosurgery. A 2007 guideline from the American Heart Association recommends antibiotic prophylaxis for dental procedures that involve oral mucosa perforation or gingival manipulation only in the following high-risk patients: CHD, prosthetic cardiac valve, unrepaired cyanotic CHD (including palliative shunts and conduits), repaired CHD with residual defect at the site of prosthetic material, previous IE, cardiac transplant with subsequent development of cardiac valvulopathy, and completely repaired cardiac defect with prosthetic material during the first 6 months after repair.

Lessons for the Clinician

- Given the prevalence of non–cardiac disease–associated endocarditis, consider risk factors such as prematurity, history of indwelling catheters, and recent skin and soft tissue infections as potential inciting events.
- When evaluating a patient with encephalopathy, clinicians should reassess the history and physical examination and broaden the differential diagnosis when the most common infectious disease, neurology, or rheumatology causes are not apparent on evaluation or the patient fails to fit the expected clinical course.
- Antibiotic prophylaxis for dental procedures involving manipulation of the gingiva or oral mucosa perforation is recommended only in patients at high risk for infectious endocarditis.

Suggested Readings

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3

Progressive Leg Pain and Weakness in a 16-year-old Boy

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AUTHOR DISCLOSURE Drs Begley, Briggs, and Williams have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 16-year-old boy presents with progressive lower extremity pain and weakness. One month ago, the patient joined the basketball team after living a sedentary lifestyle. Since then, he has developed shin splints and a dull aching pain in his ankles and lower back. He treated the pain with ibuprofen and stretching exercises, resulting in some relief. The day before admission he had severe pain in his hamstrings and also developed lower extremity weakness and numbness during practice. On the morning of admission, his symptoms are too severe for him to be able to walk.

The patient states that his pain is predominantly in his hamstrings and that he feels a "pulling sensation." He also complains of bilateral numbness and cold sensitivity on his posterior calves and on his feet below the ankles. He recently had coldlike symptoms with no other recent illnesses. He admits to losing 10 lb (4.5 kg) in the past month, which he attributes to participating in daily conditioning exercises. He denies any recent urinary symptoms.

Physical examination reveals a large teenage boy, mildly somnolent from narcotics given for pain. Vital signs show a normal temperature, blood pressure of 130/70 mm Hg, weight of 250.4 lb (113.6 kg), height of 6 feet 6 inches, and BMI of 28.89. Bruises in various stages of healing are present on the lower extremities. Dorsalis pedis pulses are intact bilaterally. Examination of the back reveals mild tenderness to palpation of the lumbar spine; however, he has no paraspinal muscular tenderness, no obvious swelling, and no bruising. Patellar and Achilles reflexes are 2+ bilaterally. No cremasteric reflex or anal tone is performed. Strength for hip flexion is 4/5 bilaterally, knee extension is 5/5 bilaterally, knee flexion is 4/5 bilaterally, ankle plantar flexion is 1/5 bilaterally, and ankle dorsiflexion is 1/5 bilaterally. Sensation to light touch is intact throughout the lower extremities.

Laboratory evaluation shows normal values for complete blood cell count, serum electrolytes, blood urea nitrogen, and creatinine. The serum creatine kinase level is 452 U/L (7.55 μkat/L) (reference range, 38–176 U/L [0.63–2.94 μkat/L]) and the C-reactive protein is 0.4 mg/L (3.8 nmol/L).

He is hospitalized for further evaluation.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/2/94.

DISCUSSION

Over 48 hours, the patient had progression of his symptoms, with increasing weakness in the distal lower extremities and loss of Achilles reflexes. He also complained of roving numbness, sometimes involving the calves and other times the hamstrings. Because of progressive neurologic findings on examination, a magnetic resonance image (MRI) was ordered.

An MRI of the lumbar spine was initially attempted without sedation, but the patient was unable to tolerate the study secondary to severe radiating bilateral hip pain while lying prone. The MRI was, therefore, performed under sedation and revealed L3-4 disk extrusion with impingement on the cauda equina, as well as hydronephrosis with distended urinary bladder, all consistent with cauda equina syndrome (CES) (Fig). In the postanesthesia care unit after the MRI was performed, he developed urinary retention and inability to void and, therefore, required Foley catheter placement.

The Condition

A rare syndrome, CES develops in 4 to 7 in 10,000 to 100,000 individuals, with disk herniation a cause in 1% to 2% of those cases. (1)(2)(3) Usually CES affects middle-aged men in their 40s and 50s, although trauma-related CES is not age specific. The spinal cord ends at the L1 vertebral level. Below this, the lumbosacral roots form the cauda equina in a common sack, which is responsible for motor and sensory function in the legs and bladder. Findings are usually consistent with injury to spinal roots rather than the spinal cord. Most injuries at the level of L2 injure the conus medullaris.

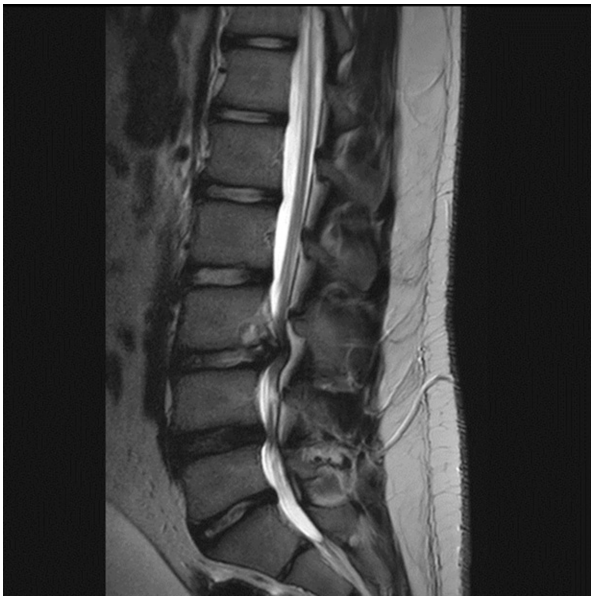

Figure. T2-weighted magnetic resonance image without contrast of the midline sagittal spine showing the disk extrusion at L3-4 and the diffuse disk bulge at L4-5.

Cauda equina syndrome is defined by a loss of function in 2 or more of the 18 nerve roots that compose the cauda equina. Symptoms of CES (1)(2) are low back pain accompanied by radiation of pain into the legs; weakness of plantar flexion of the feet with S1, S2 root involvement, with higher levels leading to weakness in corresponding muscles; bladder and rectal sphincter paralysis with involvement of S3-5 nerve roots; sensory loss in the dermatomal distribution of affected nerve roots; and sexual dysfunction of sudden onset.

Etiologies for CES include epidural tumor or abscess, intervertebral disk herniation, intradural extramedullary tumor, lumbar spine spondylosis, and carcinomatous meningitis. (1)(2)

In our patient, disk herniation caused by a sudden increase in activity/stress resulted in compression of the nerve roots in the lumbar spine.

Diagnosis of CES is difficult because symptoms vary in intensity and evolve slowly over time. (3)(4) In addition, the use of narcotics for pain control can complicate making the correct diagnosis. Diagnosis can be made by a good history and physical examination with appropriate imaging studies, such as computed tomography, MRI, or myelography.

Differential Diagnosis

Spinal tumors, direct trauma, inflammatory conditions such as ankylosing spondylitis, chronic tuberculosis, Guillian Barre syndrome, neuropathy, acute flaccid myelitis, transverse myelitis, and conus medullaris syndrome are some of the conditions that should be considered in a patient with this presentation.

Management

Cauda equina syndrome is considered a neurosurgical emergency because the amount of time before decompression directly affects the recovery of neurologic function, with an increased risk of permanent damage after 48 hours. Bowel and bladder function may take years to recover, but function may continue to improve over a long duration after decompression. Use of corticosteroids is controversial, and more research is needed to ascertain the role of corticosteroids in the management of CES. Left untreated, CES may cause paraplegia.

Patient Course/Management

The patient was transferred to a tertiary care center and taken for emergency L3-4 diskectomy with laminectomy by a pediatric neurosurgeon. After the surgery, the patient was transferred to an inpatient pediatric rehabilitation facility. Over 2 months, the patient did have sexual function (per the neurosurgeon) and was able to ambulate with assistance. He still requires intermittent self-catheterization for neurogenic bladder. He also requires numerous medications for persistent neurogenic bowel. The patient was discharged from the hospital with plans for continued intensive outpatient therapy.

Lessons for the Clinician

- Progressing neurologic symptoms need urgent evaluation and reevaluation as the amount of deficit at the time of surgery often dictates the chance of recovery.
- Cauda equina syndrome is considered a neurosurgical emergency.

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4 Poor Feeding and Lethargy in a 32-day-old Infant

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AUTHOR DISCLOSURE Drs Peebles, VanHooren, Gunz, and Salvadori have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 32-day-old boy presents to the emergency department with a 12-hour history of poor feeding and lethargy. The child was born at 34+1 weeks and spent 2 weeks in the NICU, where he was fed infant ready-made formula by gavage feeding as he gradually increased his suckling. He was discharged 5 days before his presentation.

On assessment, he is noted to be pale, hypotonic, and irritable. He is hypothermic, with a rectal temperature of 97.0°F (36.1°C). His heart rate is 150 beats/min, and capillary refill is noted to be appropriate.

A full sepsis evaluation is performed. White blood cell count is 20,000/μL (20×10^{9}/L), hemoglobin is 9.3 g/dL (93 g/L), and platelet count is 63×10^{3}/μL (63×10^{9}/L). Cerebrospinal fluid analysis shows a white blood cell count of 10,000/μL (10×109/L), a protein level of 1,650 g/dL (16,500 g/L), and a glucose level of 5.6 mg/dL (0.31 mmol/L). He is started on ampicillin, cefotaxime, and acyclovir. Within 5 hours of admission, he becomes mottled and tachycardic (190 beats/min), with intermittent apneas requiring PICU admission. Gram-negative bacilli are identified on gram stain in the cerebrospinal fluid (CSF) 6 hours after presentation; the acyclovir is stopped, and the antibiotics are changed to meropenem.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/2/95.

DISCUSSION

The organism isolated from blood and CSF on the day of admission was *Cronobacter sakazakii*.

Any neonate presenting with fever or hypothermia should undergo a full sepsis evaluation, including a lumbar puncture. The most common bacteria causing sepsis and meningitis in the neonatal age group are group B *Streptococcus, Escherichia coli,* and *Listeria monocytogenes*. Appropriate empirical antibiotics for presumed sepsis in neonates include ampicillin and cefotaxime. In cases in which an infant worsens on standard therapy, when the infant is seriously ill and standard therapy has been considered, or when a resistant gram-negative organism is isolated, therapy can be changed to meropenem. In our institution, use of meropenem mandates an infectious disease consultation.

Brain abscess is a rare complication of meningitis and is more common in premature or immunocompromised infants. In neonates, gram-negative species predominate as causative organisms, and *Enterobacteriaceae, Citrobacter* species, *Serratia marcescens, Proteus mirabilis,* and *Pseudomonas aeruginosa* have been reported. There are case reports of *Staphylococcus aureus* and *Clostridium septicum* causing brain abscesses. The presentation of a brain abscess can be nonspecific and include fever, irritability, temperature instability, apneas, and seizures. The differential diagnosis is broad and includes infectious etiologies such as meningitis, encephalitis, and subdural/epidural empyema as well as noninfectious etiologies such as neoplasms, intracranial hemorrhages, strokes, and toxic ingestions. Imaging studies are, therefore, paramount in making the diagnosis and should be performed on all neonates diagnosed as having gram-negative meningitis.

The most sensitive imaging modality for diagnosing brain abscesses is MRI. Brain abscess appears as a ring-enhancing lesion on MRI. Findings from MRI early in the course can be nonspecific, with high T2-weighted signal intensity; however, as the abscess forms, MRI reveals a ring-enhancing lesion. Diffusion-weighted imaging and magnetic resonance spectroscopy can help distinguish pyogenic abscesses from other ring-enhancing lesions such as tumors or tubercular abscesses.

The Condition

Cronobacter species are gram-negative bacteria that form a newly defined genus, formerly *Enterobacter sakazakii*. Neonatal infections with *Cronobacter* species are rare, with less than 150 cases ever reported globally in infants up to 2 months of age. Severe disease manifestations include meningitis, bacteremia, and necrotizing enterocolitis. Neonatal meningitis due to *Cronobacter* is associated with a high prevalence of brain abscess, cyst formation, infarctions, a high mortality rate (40%–80%), and long-term neurologic sequelae in survivors. Whenever *C sakazakii* is isolated from neonatal blood or CSF, serial MRIs should be performed to evaluate for abscess formation and guide optimal management. Infants at greatest risk include those who are preterm, low birthweight (<2,500 g), or immunocompromised.

Neonatal infections with *C sakazakii* have been linked to powdered formulas, including infant formulas, follow-up formulas, and human milk fortifier. Manufacturing methods used today to produce powdered formula do not produce sterile formula, and inappropriate handling practices can exacerbate this. Health organizations have advised against feeding powdered formula to premature or immunocompromised babies because of the risk of *C sakazakii* and other bacterial infections. Contamination can take place at the source (contaminated raw materials or manufacturing surfaces) or at home (contaminated preparation surfaces, water, or bottles). In recognition of the risks posed by contaminated powdered infant formula, the World Health Organization has issued guidelines for the preparation of powdered formula in health-care settings and at home. These stress the importance of hand washing and sterilization of equipment, preparing formula with boiled water, and feeding formula immediately (once cooled) or refrigerating promptly for use within 24 hours.

It is important for pediatricians to be aware of this infection because it often has devastating outcomes and for infants at greatest risk (ie, those in NICUs) is the rationale behind many recommendations regarding infant feeding practices, especially in hospitals.

Patient Course

On day 4 of admission he had a generalized tonic-clonic seizure and was loaded with phenobarbital. He underwent MRI, which showed generalized edema and restricted diffusion of the left cerebral hemisphere with asymmetric mass effect. On day 14, he became increasingly lethargic. An urgent computed tomographic scan of his head showed a large cerebral abscess in the left cerebral hemisphere causing significant mass effect with brainstem distortion (Fig). A therapeutic ventricular tap was performed. The CSF was again purulent (white blood cell count, 5,000/μL [5×109/L]; protein level, 1,455 g/dL [14,550 g/L]; and glucose level, 5.6 mg/dL [0.31 mmol/L]). Based on worsening neurologic status despite maximal therapy, his poor prognosis was discussed with his parents and a course of palliation was begun. The child died 4 days later. On review of this infant's feeding history, no breaches of infection control practice or exposure to powdered formula could be ascertained.

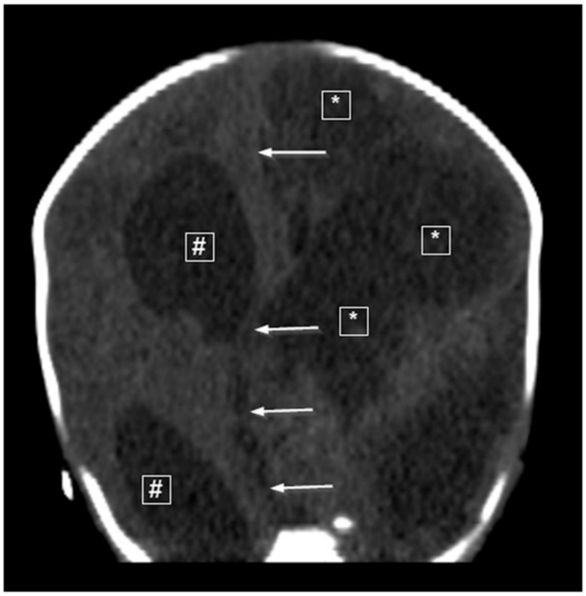

Figure. Computed tomographic scan of the head demonstrating a large fluid collection with irregular margins in the left cerebral hemisphere consistent with cerebral abscess (*). The abscess is noted to be causing significant mass effect with midline shift (arrows) causing secondary compression of the ventricular system with evidence of ventricular dilation over the right hemisphere (#).

Lessons for the Clinician

- *Cronobacter sakazakii* is a rare cause of devastating neonatal infections.
- Powdered infant formula is not sterile, and strict guidelines exist for preparation and storage to minimize the risk of bacterial contamination.
- If alternatives to human milk are necessary, liquid infant formula should be used for infants at greatest risk (ie, those in NICUs).
- Any infant who grows *Cronobacter* species from any sterile site should undergo a full sepsis evaluation (including lumbar puncture) and brain imaging.
- Brain imaging is an important component of therapy and should be performed in all neonates with focal symptoms related to meningitis and in those with certain pathogens, especially *Enterobacteriaceae*. Follow-up imaging should be performed before stopping therapy.

Suggested Readings

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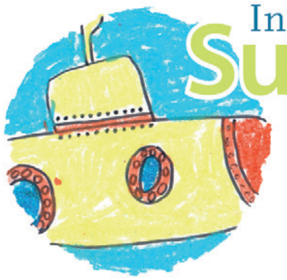

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5

Prolonged Fever in a 5-year-old Girl of Myanmese Descent

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AUTHOR DISCLOSURE Dr Bula-Rudas has disclosed no financial relationships relevant to this article. Dr Rathore has disclosed that he serves as principal investigator on research grants from GSK, Gilead Sciences Inc, and Pfizer. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-year-old previously healthy girl of Myanmese descent who was born in the United States and has never left the country presents with a 12-day history of high fevers and no other associated signs or symptoms.

On day 5 of fever she was diagnosed as having “the flu” by her pediatrician and was managed symptomatically. On day 9 of the illness she was again evaluated because of persistence of fever. There were no new physical findings. The complete blood cell count and chest radiograph were reported as normal, and a 5-day course of azithromycin was prescribed. There was no specific diagnosis documented in her records for this antibiotic course. She completed 3 days of therapy before hospital admission, and she had no improvement of her fevers.

Because of persistence of fever for 12 days she is hospitalized. Her temperature at the time of admission is 105.8°F (41°C). Physical examination findings are normal except for fussiness. But when observed from outside the room through a window she is calm and comfortable and interacting with her mother.

Laboratory evaluation shows a white blood cell (WBC) count of 12,340/μL (12.34×10^9/L) (75% neutrophils, 18% lymphocytes, and 7% monocytes), a hemoglobin level of 12.4 g/dL (124 g/L), a hematocrit value of 37.4%, and a platelet count of 53×10^3/μL. Her erythrocyte sedimentation rate is 49 mm/hour and C-reactive protein level is less than 0.5 mg/dL (<4.8 nmol/L). Serum electrolyte levels are essentially normal except for low carbon dioxide levels of 17 mEq/L (17 mmol/L). Results of polymerase chain reaction (PCR) studies for influenza, respiratory syncytial virus, parainfluenza, adenovirus, and human metapneumovirus are negative. A repeated chest radiograph shows no cardiopulmonary abnormalities. Urine and blood culture are sent and ultimately show no growth. A tuberculin skin test (TST) is nonreactive. The patient continues to spike daily fevers, and her examination results remain unchanged. She remains in the hospital for monitoring of fever and a stepwise approach to evaluate the cause of her fevers. A variety of tests and imaging studies are performed to rule out infectious diseases.

On day 19 of the illness (day 7 of the admission) she becomes encephalopathic. A computed tomographic (CT) scan of the head without contrast is normal. Cerebrospinal fluid (CSF) has a WBC count of 150/μL (0.15×10^9/L) (85% lymphocytes, 5% neutrophils, and 10% monocytes) and a red blood cell count of 4/μL ($0.04\times10_9$/L). Her CSF glucose level is 23 mg/dL (1.28 mmol/L), with a blood glucose level of 120 mg/dL (6.66 mmol/L) and a protein level of 0.118 g/dL (1.18 g/L). Findings from CSF Gram-stain and acid-fast bacilli (AFB) smear are negative. Results of herpes simplex virus and enterovirus PCR in the CSF are also negative. Magnetic resonance imaging (MRI) of the brain with contrast shows multifocal areas of hyperintense flair signal and restricted diffusion suggestive of encephalitis. There is no evidence of cerebral abscess. She develops seizures and is transferred to the ICU. On day 20 of the illness, a blood test result is reported to be positive.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/2/96.

DISCUSSION

An interferon-γ release assay (IGRA) for tuberculosis (TB) was reported to be positive and helped us establish a diagnosis of TB meningitis.

The diagnosis of TB meningitis in children is challenging and requires a high index of suspicion. The evaluation of this child with fever of unknown origin warranted a comprehensive laboratory evaluation that included a TB test. The differential diagnosis of prolonged fever includes malignancies, autoimmune diseases, and infections. Being that infections are the most common cause of fever of unknown origin in children, we initiated an evaluation for an infectious etiology. The mother denied having pets at home or contact with animals. Monospot for Epstein-Barr virus, *Bartonella* serology, and human immunodeficiency virus antigen/antibody were negative. Sinus CT, total abdominal ultrasonography, and echocardiography were performed, and all the results were normal. The only abnormal sign in this child was the fever, and not until day 19 of the illness did she became encephalopathic. The CSF analysis raised the suspicion for TB meningitis; therefore, anti-TB treatment with rifampin, isoniazid, pyrazinamide, and amikacin was started, along with corticosteroids. At this time the TST was nonreactive and the IGRA was pending. The IGRA was sent around the same time of TST placement. This child's parents are immigrants from Myanmar. The mother denied exposure to TB on several occasions to several physicians. When the IGRA was reported positive, she then disclosed a close contact of the family as having active TB currently on treatment. The mother reported that she was afraid of disclosing this contact because of fear for this person losing his or her job in a supermarket. There was also a language barrier when interviewing the mother. A live interpreter was used at the time of admission and for the infectious diseases initial interview, but a telephone service interpreter line was used for subsequent visits. The child did not speak English.

The Condition

Tuberculous meningitis accounts for high morbidity and mortality rates in the pediatric population, especially in infants and young children. Children aged 6 months to 4 years are most commonly affected. Diagnosing TB meningitis is challenging in all age groups. The clinical features can appear rapidly or gradually. Infants and young children present more commonly with rapid progression. Involvement of the central nervous system (CNS) occurs either from a renewed activity of an early established caseous lesion in the cerebral cortex or meninges or from direct invasion that occurs during dissemination. The basilar area of the brain is most commonly affected. Basilar meningitis is common and frequently leads to communication hydrocephalus. Basilar meningitis may also contribute to cranial nerve palsies involving cranial nerves III, VI, and VII. Involvement of the blood vessels may lead to vasculitis and cerebral infarction. Children can present with subtle signs such as low-grade fevers, malaise, irritability, and anorexia. Neurologic signs are usually not present in the early stages of the illness and may not become evident until there are focal deficits, behavioral changes, or comatose appearance. Seizures are more common in children than in adults. To categorize children with TB meningitis, a staging system has been used since the 1960s. This 3-stage system is based on neurologic findings. In stage I there are nonspecific signs and symptoms, and there is no evidence of neurologic involvement; this stage can last up to 2 weeks. Stage II is characterized by more abrupt changes, and 2 scenarios can occur: change in the sensorium with or without focal neurologic signs, or no change in the sensorium but focal neurologic deficit. Stage III presents with more devastating signs, such as coma, decorticate posturing, and abnormalities of vital signs, which can progress to death.

Diagnosis

For diagnosing any form of TB, both the TST and the IGRA have many limitations, particularly in children. The TST placement and interpretation are difficult. The IGRAs are easy to obtain and are more specific than the TST, but interpretation has not been well established in younger children. The IGRAs measure ex vivo interferon-γ production from T lymphocytes in response to stimulation with antigens specific to the *Mycobacterium tuberculosis* complex (*M tuberculosis* and *Mycobacterium bovis*). The IGRAs are reliable in children 5 years and older. Routine testing with both TST and IGRA is not recommended. However, sensitivity to diagnose TB increases when both TST and IGRAs are performed together. Using both also increases the rate of positive results in patients at high risk for TB. The IGRAs have been reported to be more specific than TST in children despite all the limitations. The IGRAs have higher specificity than TST when a child had been immunized with bacillus Calmette-Guérin because they do not test for antigens included in this vaccine.

The diagnosis of TB meningitis is usually suspected once neurologic signs appear. The CSF profile can help with the diagnosis. The presence of lymphocyte-predominant pleocytosis (WBC count, 100–500/μL [$0.10–0.50 \times 10^9$/L]), elevated protein levels (0.100–0.500 g/dL [1.00–5.00 g/L]), and low glucose levels (usually ≤45 mg/dL "[≤2.5 mmol/L]) suggest TB meningitis. Sometimes protein levels in the CSF are greater than 0.400 g/dL (>4.00 g/L). A single CSF sample has low sensitivity (20%–40%) for detecting AFB in the smear. Higher volumes of CSF increase the yield for AFB detection. The AFB culture can take several weeks, and sensitivity is low as well (40%–80%). Nucleic acid amplification assays in the CSF have specificity of 98%, although overall sensitivity is approximately 56%.

Both CT scans and MRIs can show pathologic changes of TB meningitis and may provide important information for prognosis as well as diagnose complications of TB meningitis. Basal enhancement, hydrocephalus, tuberculoma, and infarction are findings more commonly seen in CT scans of children with TB meningitis, whereas subdural collections are more common in those with pyogenic meningitis. Recent data suggest that precontrast hyperdensity in the basal cisterns is the most specific radiologic sign of TB meningitis in children.

Treatment and Prognosis

Treatment of TB meningitis in children is still controversial. The American Academy of Pediatrics recommends the use of 4 drugs: rifampin, isoniazid, pyrazinamide, and ethionamide or an aminoglycoside. Once susceptibilities are determined, the ethionamide or the aminoglycoside can be discontinued. Pyrazinamide and ethionamide or an aminoglycoside are given for 2 months, and rifampin and isoniazid are given for 9 to 12 months. The use of adjunctive corticosteroids is definitively recommended in children. Corticosteroids reduce mortality but not morbidity. Diagnosing TB meningitis in the earlier stages is important for preventing the associated neurologic morbidity. The prognosis is poor when the diagnosis is made in stage III.

Patient Course

The patient's neurologic status deteriorated. She remained comatose with decorticate posture. The CSF culture grew *M tuberculosis* after 1 month of incubation, and it was confirmed by PCR. She was transferred to a rehabilitation facility and was discharged after completion of an assessment for establishing a long-term plan for care of a medically complex patient with a poor neurologic prognosis.

Lessons for the Clinician

- Evaluation of fever of unknown origin should follow a tiered approach.
- Pulmonary and extrapulmonary tuberculosis (TB) should be considered in the differential diagnosis of fever of unknown origin in children.
- Both a tuberculin skin test and an interferon-γ release assay (IGRA) increase the positive predictive value when used in combination in children at higher risk for TB.
- Conducting a complete TB screening questionnaire is very important in any child with risks for TB infection.
- A positive IGRA result in an infant or young child likely indicates infection with *Mycobacterium tuberculosis,* but a negative result does not rule it out.

Suggested Readings

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6 An Infant Presenting with Hematuria and Pallor

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AUTHOR DISCLOSURE Drs Riney, Treasure, Varnell, and Depinet have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-month-old healthy boy presents to our pediatric emergency department with parental concerns of blood in the urine and yellow appearance of the skin. His medical history and birth history are normal. The patient has had nonbloody diarrhea for the past 2 weeks that resolved 2 days ago. He has had 1 episode of nonbilious nonbloody emesis the previous day. In addition, he has had decreased oral intake and increased fussiness for the previous 2 days. His mother noticed a red-brown discoloration in the front of the diaper yesterday and yellow discoloration of the skin, prompting her to present to the pediatric emergency department.

Vital signs at presentation are heart rate, 157 beats/min; respiratory rate, 42 breaths/min; blood pressure, 127/70 mm Hg; and rectal temperature, 97.9°F (36.6°C). On initial examination in the emergency department, the patient is pale but alert, active, in no apparent distress, and playful. His mucous membranes are moist, and his oropharynx is normal, without lesions. The cardiovascular examination reveals a regular rate and rhythm, without murmurs, rubs, or gallops. He has strong peripheral pulses and good distal perfusion. His pulmonary examination findings are normal. His abdomen is soft, nondistended, and nontender, with normal bowel sounds. Neurologic examination shows symmetric normal strength and tone with grossly intact cranial nerves and no deficits. Skin examination shows generalized pallor but no rash or petechiae. Both feet seem to be mildly edematous.

Pertinent laboratory studies in the emergency department show a white blood cell count of 27,200/μL (27.2×10^9/L) (reference range, 6,000–17,500/μL [6.0–17.5×10^9/L]), with 38% segmented neutrophils and 2% bands; a hemoglobin level of 3.7 g/dL (37 g/L) (reference range, 10.5–13.5 g/dL [105–135 g/L]); a hematocrit level of 10% (reference range, 33%–39%); and a platelet count of $38\times10^3/\mu$L ($\times10^9$/L) (reference range, $13.5\times10^3/\mu$L–$46\times10^3/\mu$L [$\times10^9$/L]). In addition, the blood smear shows 2+ schistocytes, 1+ ovalocytes, and 1+ teardrops. The renal panel is significant for a potassium of level of 6.9 mEq/L (6.9 mmol/L) (reference range, 3.2–6.3 mEq/L [3.2–6.3 mmol/L]), a blood urea nitrogen level of 59 mg/dL (21.1 mmol/L) (reference range, 6–17 mg/dL [2.1–6.1 mmol/L]), and a creatinine level of 0.95 mg/dL (72.44 μmol/L) (reference range, 0.16–0.39 mg/dL [12.20–29.74 μmol/L]).

The hepatic profile is normal. The urinalysis was significant for large blood and large protein with 10 to 14 white blood cells and greater than 50 red blood cells per high-power field and 2+ bacteria.

Because of severe anemia, thrombocytopenia, hyperkalemia, and acute kidney injury, the patient is admitted to the PICU and the nephrology team is consulted. Additional studies lead to the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/2/98.

DISCUSSION

While in the PICU, further laboratory studies showed a lactate dehydrogenase level of 1,704 U/L (28.5 μkat/L) (reference range, 155–450 U/L [2.6–7.5 μkat/L]), a haptoglobin level less than 7 mg/dL (<70 mg/L) (reference range, 16–200 mg/dL [160–2,000 mg/L]), a reticulocyte count of 5.3% (reference range, 0.5%–1.5%), a C3 complement level of 1.24 g/L (reference range 0.624 g/L–1.84 g/L), and ADAMTS13 activity of 92% (reference range, >67%). The stool culture grew *Escherichia coli* 0157:nonH7 and Shiga toxin 2 three days later. The urine culture showed no growth after 5 days. A diagnosis of hemolytic uremic syndrome (HUS) was made.

The Condition

Hemolytic uremic syndrome is a type of thrombotic microangiopathy, a heterogeneous group of diseases that have common clinical manifestations, including microangiopathic hemolytic anemia, thrombocytopenia, and organ injury. (1)(2) Classically, HUS presents as severe abdominal pain and diarrhea, often bloody, that begins several days after consumption of food contaminated with Shiga toxin–producing *E coli* (STEC). (3) Hemolytic uremic syndrome should be suspected in any pediatric patient with recent abdominal pain and diarrhea followed by thrombocytopenia and anemia 5 to 7 days later. (1) Other clinical signs during this period may include hypertension, oliguria, central nervous system manifestations, altered mental status, and possibly more severe gastrointestinal manifestations (ischemic bowel or intussusception). (4) After a few more days, anuria may develop, and the clinical picture can change to include coma, cerebral infarcts, cranial nerve dysfunction, seizures, and even death. (2)(4) Laboratory studies that should be performed on presentation are as follows: a complete blood cell count, a peripheral blood smear, renal function studies, and urinalysis. (5) Other initial testing includes coagulation studies (to differentiate from disseminated intravascular coagulation) and stool studies for Shiga toxin and cultures. (5) Shiga toxin–producing *E coli* accounts for almost 90% of all cases of HUS, with occurrence usually younger than 5 years, most being older than 6 months. (2)(3)

History has shown that young children and elderly people can have substantial impairment from infection with STEC. (6) Approximately 5% to 10% of people with STEC infection will go on to develop HUS, and 50% of those will have some degree of renal impairment after disease. (2)(6) The severity of the acute illness and the need for initial dialysis are strongly linked to a poor long-term prognosis. (7) Hemolytic uremic syndrome should be considered for any child with a history of resolving diarrhea now with concern for kidney injury given that it is a common cause of acute renal failure worldwide. (8)

Diagnosis

The diagnosis of HUS is based on laboratory findings, although it does require a certain level of clinical suspicion, particularly given a well-appearing child with only a history of previous diarrheal illness. The most common laboratory findings are hemolytic anemia, thrombocytopenia, and renal dysfunction. (9) More specifically, the anemia found in HUS is a normochromic-normocytic anemia, with an average hemoglobin level of 8 g/dL (80 g/L). (4) Additional laboratory findings that are often seen include azotemia, a decreased haptoglobin level, an elevated C-reactive protein level, hematuria and/or proteinuria on urinalysis, an increased lactate dehydrogenase level, leukocytosis, an elevated reticulocyte count, and a negative Coombs test result. (9) The first signs of renal involvement are typically hypertension, (seen in nearly 50% of patients with HUS), hematuria, and proteinuria. (4) Severe renal disease is characterized by anuria and renal failure. (4) More commonly, however, patients experience a brief period of oliguria (median of 7 days) with associated electrolyte abnormalities, including hyponatremia, hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. (4) A stool culture should be obtained in any patient suspected of having HUS to evaluate for the presence of STEC, which is a reportable illness and has implications for morbidity and mortality. (9)

Stool cultures were sent as well as enzyme immunoassay for Shiga toxin 1 and Shiga toxin 2 to assess for STEC-HUS. ADAMTS13 activity was sent to assess for thrombotic thrombocytopenic purpura (TTP) and in our patient was normal. The other major consideration in this patient was atypical HUS (aHUS). Given that the patient's disease was relatively mild on hospital admission, with a stable elevated creatinine level and good urine output, aHUS genetic testing was deferred unless the testing for Shiga toxin came back negative. Current diagnostic criteria for aHUS are a serum creatinine level at or above the upper limit of normal, microangiopathic hemolytic anemia, thrombocytopenia, ADAMTS13 activity of 5% or more, and negative stool tests for Shiga toxin–producing infection. Our patient's stool culture was positive for *E coli* 0157:nonH7 and Shiga toxin 2, thus, further treatment was supportive in nature.

Differential Diagnosis

In a pediatric patient presenting with a recent diarrheal illness, the differential diagnosis is broad and includes viral or bacterial gastroenteritis, colitis, inflammatory bowel disease, or intussusception. (9) In a pediatric patient presenting with laboratory findings of severe anemia, thrombocytopenia, and concern for acute kidney injury, the differential diagnosis is relatively narrow. Three diseases that were initially considered that could describe the patient's presenting symptoms include HUS, aHUS, and TTP.

By definition, aHUS is not preceded by the characteristic bloody diarrhea of STEC infection, but because most cases of aHUS involve dysregulation of the complement system it is frequently triggered by an infectious event, including gastroenteritis with diarrhea. (10) Commonly, TTP, which is rare in children, is caused by congenital mutation in the *ADAMTS13* gene, a plasma metalloprotease that cleaves von Willebrand factor. (1)

Management

There are no known cures for HUS, and management is primarily supportive. Given the wide range of illness severity, it is important that patients diagnosed as having HUS are closely monitored for anemia, electrolyte disturbances, and acute renal failure. Fluid balance before and after the development of HUS has been shown to be important in limiting the severity of renal failure and the need for dialysis. (9) The decision to start dialysis is based on the ability to correct renal failure and electrolyte abnormalities with fluid replacement alone. (4) Approximately 50% of patients will require dialysis at some point during the illness, with approximately 7.6% going on to require dialysis long-term. (8) In addition, studies have shown that more than 90% of patients diagnosed as having HUS will require a blood transfusion during the course of the illness. (8) Regarding the finding of thrombocytopenia in HUS, platelet transfusions are not routinely given due to the worsening of the thrombotic cascade, and platelet function typically normalizes after several weeks. (4) Interestingly, the use of antibiotics has been studied in patients diagnosed as having HUS and in some studies has been shown to actually increase the incidence and complications of HUS when given during the diarrheal stage of the illness. (2)(3) The worsening of disease is believed to be secondary to the release of large amounts of bacterial toxins with the use of antibiotics. (2)(3)

Patient Course

During his PICU admission, the patient remained hemodynamically stable. He was given calcium chloride 10 mg/kg intravenously for cardiac membrane stabilization. He was kept nothing per os and started on 10% dextrose 1/2 normal saline for insensible losses at 10 mL/kg as well as replacement fluids for urine output every 6 hours. Furosemide 2 mg/kg was given intravenously due to hyperkalemia and concern for blood transfusion exacerbating his hyperkalemia. Slow correction of anemia was performed to prevent massive hemolysis. He was given 2 intravenous transfusions of packed red blood cells 5 mL/kg each. No antibiotics were given. No antihypertensives were needed because the systolic blood pressure remained less than 130 mm Hg and trended down during the admission, although still elevated for his age. Daily weights were obtained, strict intake and output were recorded, and nephrotoxins were avoided. He had good urine output during his admission. He was transferred from the PICU after 2 days to the nephrology service and was discharged after 5 days.

The patient had return of normal renal function at his nephrology outpatient visit 48 days after his initial diagnosis of Shiga toxin–positive HUS. Blood pressure was 82/50 mm Hg, which was 37 percentile systolic for age and 88 percentile diastolic for age, based on the 2000 National Health and Nutrition Examination Survey data. Laboratory studies showed normalization of his electrolytes, blood urea nitrogen, creatinine, hemoglobin, and platelets. Urinalysis was negative for proteinuria and hematuria. He had no evidence of chronic kidney disease at further follow-up visits with the nephrology service.

Lessons for the Clinician

- Hemolytic uremic syndrome is one of the most common causes of acute renal failure in the pediatric population worldwide, and its rising incidence makes it an important diagnosis to consider. (11)
- Although hemolytic uremic syndrome is a disease with specific laboratory criteria, the wide variance of clinical presentations and multiple etiologies of the illness can make it difficult to diagnose.

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in Brief

Cyclic Vomiting Syndrome

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Treatment of Cyclic Vomiting Syndrome with Co-enzyme Q10 and Amitriptyline, a Retrospective Study. Boles RG, Lovett-Barr MR, Preston A, Li BU, Adams K. *BMC Neurol.* 2010;10:10

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Cyclic Vomiting Syndrome: What a Gastroenterologist Needs to Know. Pareek N, Fleisher DR, Abell T. *Am J Gastroenterol.* 2007;102(12):2832–2840

Cyclic vomiting syndrome (CVS) is characterized by recurring, intense episodes of nausea and vomiting lasting hours to days, separated by weeks to months of symptom-free, normal health. The prevalence of CVS is approximately 1% to 2%, and it affects multiple ethnicities and ages, most frequently white school-aged children. From the onset of symptoms, diagnosis can be delayed by an average of 1 to 4 years. Episodes result in approximately a month's worth of missed school days annually and an estimated $17,000 in yearly health-care costs, multiple emergency department visits, and repetitive testing.

Cyclic vomiting syndrome and migraines seem to be linked in both pathophysiology and treatment, and familial history of migraine is often noted. Several etiologic hypotheses exist, but none are proved. The potential causative factors include mitochondrial DNA polymorphisms/variants, excessive secretion of adrenocorticotropin-releasing factor, dysmotility of the gastrointestinal system, and autonomic (particularly sympathetic) nervous system dysregulation.

With approximately 90% specificity, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition has published a consensus statement that includes the criteria to diagnose CVS. All of the following criteria must be met: at least 5 attacks in any interval, or a minimum of 3 attacks during a 6-month period; episodic attacks of intense nausea and vomiting lasting 1 hour to 10 days occurring at least 1 week apart; stereotypical patterns and symptoms in individual patients; vomiting during attacks occurring at least 4 times per hour for at least 1 hour; a return to baseline health between episodes; and vomiting cannot be attributable to any other disorder. Although not included in the criteria, 75% of patients have been noted to have episodes early in the morning, and symptoms are often triggered by excitement, illness, or stress and lead to severe dehydration and lethargy.

Other acute, urgent disorders causing vomiting must be ruled out and can usually be excluded by history, physical examination, and basic laboratory studies, including a complete blood cell count, complete metabolic panel, urinalysis, and upper gastrointestinal series with small-bowel follow-through. A pregnancy test may be applicable. Blood samples should be collected before administration of intravenous fluids. Further investigations depend on specific history and physical examination findings, with particular attention given to red flag symptoms.

In patients with severe abdominal pain, tenderness, or bilious vomiting, providers must consider in the differential diagnosis an acute abdomen, biliary disease, hepatitis, pancreatitis, hydronephrosis, or ureteropelvic junction obstruction. In these cases, abdominal ultrasonography or computed tomographic scanning and appropriate laboratory tests (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase amylase, lipase) may be justified. Hematemesis or chronicity of unremitting symptoms may warrant upper endoscopy to evaluate for ulcers, bleeds, celiac disease, or inflammatory bowel disease. In addition, a urea breath test or biopsy to rule out *Helicobacter pylori* infection may be considered. Other suspicious symptoms deserving further evaluation include attacks with fasting, illness, or high-protein meals. Measurement of levels of serum glucose, lactate, ammonia, amino acids, plasma carnitine, acylcarnitine, urine ketones, and organic acids in this scenario may reveal a metabolic disorder. In patients with progressive neurologic symptoms or focal physical examination findings, magnetic resonance imaging of the brain should be performed. Although rare, acute intermittent porphyria also may be considered in the differential diagnosis in adolescents with concomitant anxiety, depression, or hallucinations and recurrent abdominal pain with vomiting. Urinary δ-aminolevulinic acid and porphobilinogen levels would aid in such diagnosis.

Divided into well and episodic phases, with episodic phases subdivided into prodromal, vomiting, and recovery phases, optimal treatment depends on the phase of illness. Some experts support the use of oral nonsteroidal anti-inflammatory drugs during the prodromal phase before vomiting begins. During the episodic vomiting phase, staples of treatment are supportive and abortive. Treatment includes a quiet, dark, less-stimulating environment; age-appropriate inhaled sumatriptan as abortive therapy; intravenous dextrose-containing fluids; and antiemetics (ondansetron), with the addition of sedatives such as diphenhydramine or lorazepam and analgesics such as ketorolac as needed. If these management strategies do not provide some relief to the patient, the clinician should reassess for an underlying surgical etiology. The recovery phase follows the last emesis and typically lasts a few hours as the patient states that he or she is hungry and begins to tolerate a slowly advancing oral diet.

Prophylactic treatment during periods of wellness is an option for frequent episodes or severe episodes likely to hospitalize the patient. Triggers such as excessive excitement, fatigue, stress, or fasting should be avoided. When medication is warranted, cyproheptadine is the preferred drug for prophylaxis in patients 5 years and younger, and amitriptyline for patients older than 5 years. Propranolol, an effective second-line drug, may be an alternative with a more acceptable adverse effect profile. Anticonvulsants, used for migraines, are also effective. Recent studies suggest that coenzyme Q and/or L-carnitine supplementation may be beneficial, although only limited case series and cross-sectional studies exist.

Younger age at onset of symptoms seems to correlate to longer duration of illness. However, 67% to 75% of CVS cases eventually resolve. Unfortunately, a large proportion of patients may develop migraine headaches by their late teens or adulthood.

COMMENT: Having cared for several hospitalized patients with the diagnosis of cyclic vomiting, I was struck by the intensity of the symptoms and the true misery of the patients during the duration of the emesis. Hence, it is critical to make the diagnosis, support the patient in both treatment and prevention, and try to eliminate unnecessary repetitive testing. The heterogeneity of symptoms can lead to the challenges of diagnosis, but the consensus statement by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition aids clinicians to make the diagnosis in a more timely manner. The critical need for patient and family support is apparent, and families should be guided to organizations that can provide resources, such as the Cyclic Vomiting Syndrome Association and the Gastroparesis and Dysmotilities Association, to name a few.

– Janet R. Serwint, MD
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in Brief

Human Trafficking

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ABBREVIATIONS

CSEC	commercial sexual exploitation of children
DMST	domestic minor sex trafficking
STI	sexually transmitted infection

Child Sex Trafficking and Commercial Sexual Exploitation: Health Care Needs of Victims. Greenbaum J, Crawford-Jakubiak JE. *Pediatrics.* 2015;135(3):566–574

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Human trafficking is an increasingly recognized global health crisis affecting individuals in every country and in every region of the world. Victims have been identified from more than 152 countries. The overwhelming majority of those victims are women and children. Recent reports suggest that one-third of all human trafficking victims are children. Thus, it is imperative for health-care providers to understand the very real and ever-burgeoning tragedy of modern-day slavery and how to identify children who may be at risk.

Human trafficking is defined as the "recruiting, harboring, transporting, providing, or obtaining a person for compelled labor or commercial sex acts through the use of force, fraud, or coercion" (US Department of State). Although most trafficking victims are subjected to sexual exploitation, other forms of exploitation (including forced labor, debt bondage, domestic servitude, forced child labor, and the use of child soldiers) are increasingly acknowledged.

The commercial sexual exploitation of children (CSEC) is engaging minors (<18 years of age) in sexual acts for items of value (such as food, shelter, drugs, money) that may or may not include force, fraud, or coercion.

Historically, CSEC was thought to occur primarily in other countries, and sex trafficking in the United States was thought to be solely transnational trafficking of minors from other countries into the United States. More recently domestic minor sex trafficking (DMST) has been identified; DMST is a subset of CSEC that refers to the commercial sexual exploitation of children, preadolescents, and adolescents who live in the United States. The International Labour Organization estimates that 2.5 million adults and children are at risk for trafficking worldwide, and 244,000 to 325,000 children remain at risk each year in the United States alone. This estimate is imperfect because these crimes often go undetected and victims are reluctant to self-identify for many reasons (fear of trafficker, loyalty to trafficker, lack of knowledge that they are victims, distrust of authorities, fear of arrest). Nonetheless, it is important to note that there are more children living in the United States who are sexually exploited than children who are trafficked into the United States.

Perpetrators of CSEC prey on normal developmental vulnerabilities of adolescents and include female, male, and transgender youth. Several additional factors increase the risk of involvement, including youth with a history of childhood maltreatment, running away, homelessness, substance abuse, mental health disorders, and developmental or learning disabilities. In addition, parental history of mental health disorders, intimate partner violence, and substance abuse are notable risk factors. Many victims will enter exploitation through the use of social media sites, unsupervised social settings, and the guise of romance by a trafficker.

All CSEC should be considered child sexual abuse. The victims are at risk for considerable immediate and long-term physical and mental health sequela (injuries from violence, sexually transmitted infections [STIs] and other reproductive health issues, poorly controlled chronic health conditions, substance abuse, depression, anxiety, posttraumatic stress disorder). Because many victims seek medical care for various reasons during their exploitation, health-care providers are uniquely positioned to identify potential victims and provide comprehensive physical and mental health assessment and support. Although there are no current standard screening tools, physicians should include DMST in their differential diagnosis and recognize possible indicators (tattoos, injuries, STIs). Physicians should be familiar with mandatory reporting laws, federal and state laws to protect victims of human trafficking, and local advocacy organizations. Physicians should stress that the child is a victim in need of services. The National Human Trafficking Resource Center Hotline is always available to provide information on local resources.

In 2000, the United States authorized the Victims of Trafficking and Violence Protection Act. As arguably one of the most important laws in the battle against human trafficking, it aided in defining severe forms of sex and labor trafficking. That same year, the United Nations adopted an international agreement to address the crime of human trafficking on a transnational level. This agreement, the Palermo Protocol to Prevent, Suppress, and Punish Trafficking in Persons, Especially Women and Children, has now been ratified by 169 party states.

Efforts to combat human trafficking have improved. Millions of children, however, continue to be at risk for exploitation worldwide. We need continued research and clinical work to improve the prevention, identification, and intervention of this population.

COMMENT: I found this *In Brief* on human trafficking very informative. I am amazed at the number of children who may be involved and think about countless past “missed opportunities” when I may have evaluated children and adolescents who met the risk factors but did not even consider human trafficking as a possibility. This is a critically important part of the differential diagnosis of children we evaluate who may have STIs at a young age or repetitively, in patients in whom we may suspect prostitution, in patients who are homeless, may have run away, or are suffering from mental illness. A focus on safety is a useful approach. Some questions to consider that are from the American Academy of Pediatrics Clinical Report on Child Sex Trafficking include the following:

- Has anyone ever asked you to have sex in exchange for something you wanted or needed (money, food, shelter)?
- Has anyone ever asked you to have sex with another person?
- Has anyone ever taken sexual pictures of you or posted such pictures on the Internet?

Remember that the child or adolescent is a victim, and this is a critically important area in which to be informed in our role as advocates for our patients and to identify and break the cycle of this type of maltreatment.

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Trisomies

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AUTHOR DISCLOSURE Drs Levy and Marion have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Errors in meiosis during the production of gametes lead to abnormalities of chromosome structure or number. Chromosomal abnormalities occur in 0.5% to 1.0% of live births and cause trisomy syndromes such as 21, 13, and 18.

TRISOMY 21 (ALSO KNOWN AS DOWN SYNDROME)

Occurring in approximately 1 in 700 live births, trisomy 21 is by far the most common trisomy. In 94% of patients, it is caused by nondisjunction, with 3 copies of chromosome 21 present in all cells. In 4.5% of patients, the extra chromosome 21 is part of a translocation, the most common of which involves chromosomes 14 and 21.

Although most children with trisomy 21 have normal birthweight and birth length, they have a characteristic facial appearance, which includes brachycephaly, a flattened occiput, a depressed nasal bridge, upslanting palpebral fissures, epicanthal folds, and a large protruding tongue. Other features include short, broad hands, often with a transverse palmar crease, and a wide gap between the first and second toes. Hypotonia may be severe enough to cause significant feeding problems, with some infants requiring nasogastric feeding. Individuals with trisomy 21 have many health issues. In the newborn period, concerns include the following:

1) Congenital heart disease: Approximately 40% are born with a cardiac anomaly, most of which involve abnormalities of the embryonic endocardial cushion. Atrioventricular canal, ventriculoseptal, and atrioseptal defects are the most common anomalies. All infants diagnosed as having trisomy 21 should have an echocardiogram before hospital discharge.
2) Congenital gastrointestinal defect: Five percent to 10% have an obstructive lesion of the small intestine. Duodenal atresia is most common, but annular pancreas is also seen. In addition, 2% to 5% have obstruction from Hirschsprung disease. Anal atresia can also occur. Surgery is usually necessary to repair these obstructions.
3) Hematologic abnormalities: More than 50% exhibit polycythemia (hematocrit level ≥65%). A smaller percentage has a markedly elevated white blood cell count, suggestive of congenital leukemia. Known as a leukemoid reaction or transient myeloproliferative disorder, it is benign, resolving on its own. Treatment for the polycythemia is necessary for symptoms of hyperviscosity. Trisomy 21 confers an increased risk (10- to 18-fold) of leukemia. Children younger than 1 year develop acute nonlymphoblastic forms of leukemia; older children, similar to the general population, predominantly contract acute lymphoblastic leukemia.
4) Hypothyroidism and other endocrine abnormalities: Approximately 1% have congenital hypothyroidism. The prevalence of hypothyroidism rises dramatically with age, reaching approximately 20% by 21 years old. In most patients,

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autoimmune thyroiditis is the cause. Hyperthyroidism is also more common, occurring in approximately 3%. Monitoring of thyroid function is essential in the management of children with trisomy 21. Diabetes mellitus and obesity also become more prevalent as affected children age.

Medical issues in older individuals with trisomy 21 include the following:

1) Intellectual and developmental disabilities: As in the general population, the spectrum of intellectual development adheres to a bell-shaped curve; however, with trisomy 21, the median IQ is approximately 60, rather than 100. It is essential that all children with trisomy 21 receive early intervention services, including physical, occupational, and speech therapy, as well as special instruction, and other educational services, from as early in life as is possible.
2) Other neurologic issues: There is increased risk of developing seizures early in life, especially infantile spasms, which occur in 1% to 3%. Individuals with trisomy 21 are 6 times more likely than the general population to develop a dementia-like syndrome similar to Alzheimer disease.
3) Immune function: There is greater susceptibility to infections, especially early in life.
4) Ophthalmologic: Strabismus and the development of early cataracts are more common than in the general population.
5) Otolaryngologic: Obstructive apnea, and both sensorineural and conductive hearing loss are also more common.

Individuals with trisomy 21 must be followed by a multidisciplinary team of health-care providers with expertise in the care of these children. As a guide, the American Academy of Pediatrics has published "Health Supervision for Children with Down Syndrome."

TRISOMY 18

The second most common trisomy is trisomy 18, occurring in 1 in 3,000 to 1 in 8,000 live births with a ratio of females to males of 3:1. More than 95% of trisomy 18 conceptuses are lost as spontaneous abortuses.

Only 25% to 40% of affected infants live beyond the first month, and only 2% to 8% survive past their first year. Among survivors, severe intellectual disability, coupled with serious chronic medical problems, is the rule. The decision to provide extraordinary care to infants with trisomy 18 must be tailor-made for each child, with an ongoing dialogue between the primary care provider, the multidisciplinary team, and the child's family.

Virtually all cases of trisomy 18 result from an extra copy of the chromosome; unlike trisomy 21, there are no cases from unbalanced translocations. Most affected infants are small for gestational age with a characteristic phenotype, including dolichocephaly with a prominent occiput, micrognathia with a receding jaw, short palpebral fissures, and low-set malformed ears. Additional features include a short sternum and anomalies of the feet, including prominent talus rocker-bottom feet and talipes equinovarus (club-feet). The hands are striking, with hypoplastic nails, fingers held in a clenched posture, and the second and fifth digits overlapping the third and fourth digits.

TRISOMY 13

The third most common trisomy occurs in 1 in 12,000 live births. Similar to trisomy 18, the condition is nearly always fatal in the first year of life; less than 10% of infants with trisomy 13 survive beyond their first birthday.

Generally, infants with this condition have intrauterine growth restriction and microcephaly. Midline facial defects such as cyclopia (single orbit) and cleft lip and palate are common, as well as midline central nervous system anomalies, such as alobar holoprosencephaly. The forehead is generally sloping, the ears are often small and malformed, and severe anomalies of the eyes (anophthalmia or microphthalmia) occur. Postaxial polydactyly is common, as are clubfeet or rocker-bottom feet. Hypospadias and cryptorchidism are common in males, and females generally have hypoplasia of the labia minora.

As in trisomy 18, anomalies of virtually every organ system are seen in infants with trisomy 13. Most infants have congenital heart disease. Abnormalities of the lungs, liver, kidneys, and pancreas are often seen.

GENETIC COUNSELING

The common trisomies are most often diagnosed prenatally or at birth. Because advanced maternal age is a risk for nondisjunction, prenatal testing is routinely offered to pregnant women who will be 35 years or older at their child's birth. Amniocentesis remains the gold standard for identifying fetal chromosome abnormalities, but pregnancies at risk can now be identified by noninvasive prenatal screening, which identifies fetal DNA from maternal blood.

The recurrence risk for parents with a child with trisomy 21 depends on the child's cytogenetic findings. If nondisjunction led to trisomy 21, the recurrence risk is 1% higher than the mother's age-specific risk for women younger than 35 years, and only the age-specific risk for women older than 35 years. For the two-thirds of cases when an unbalanced translocation occurs de novo, the recurrence risk is 1%. In the remaining one-third of cases, where 1 of the parents has a balanced translocation, if the mother is the carrier, the recurrence risk is 10% to 15%; if the father is the carrier, the risk is only 2% to 5%.

Genetic counseling for parents of children with trisomy 18 is similar to that in trisomy 21. Prenatal testing, as described for trisomy 21, is available.

As in the other trisomies, most cases of trisomy 13 are caused by nondisjunction, but the frequency of unbalanced translocations (20%) is higher than in trisomy 21 or trisomy 18. Recurrence risk, as with trisomy 21, increases with advancing maternal age. For prenatal diagnosis, noninvasive prenatal screening, maternal serum biochemical screening, ultrasonography, amniocentesis, and chorionic villous sampling are all available.

COMMENT: With time, and experience, our view of children with trisomies has changed, often in dramatic ways. In the past, for example, children with Down syndrome either were not considered for corrective cardiac surgery at all or their referral for surgery was commonly delayed to the point that onset of shunt reversal with pulmonary hypertension (Eisenmenger syndrome) made correction useless. Even more fundamentally, how many children with Down syndrome were in effect stockpiled in institutions to "protect" their families from having to cope with so "hopeless" a child? And we don't need long memories to recall the days when resuscitative efforts were not even a consideration for any child with trisomy 13 or 18. Change can be for the better.

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR FEBRUARY 2018 PEDIATRICS IN REVIEW

Pediatric Solid Tumors of Infancy: An Overview: 1. E; 2. C; 3. A; 4. D; 5. A.
Recognizing and Referring Children with Posttraumatic Stress Disorder: Guidelines for Pediatric Providers: 1. A; 2. B; 3. D; 4. C; 5. E.
Kawasaki Disease: 1. A; 2. C; 3. B; 4. A; 5. C.

Visual Diagnosis

A Rapidly Progressive Soft Tissue Shoulder Mass in a 3-month-old Infant

James C. League-Pascual, MD, MS,* Kip R. Hartman, MD†

*Fort Belvoir Community Hospital, Fort Belvoir, VA
†Walter Reed National Military Medical Center, Bethesda, MD

PRESENTATION

A 3-month-old healthy boy presents with parental concerns of a growing mass developing near his left shoulder. His mother reports no other unusual symptoms, such as fevers or increased fussiness. He is feeding well without difficulty and gaining weight appropriately for his age. On physical examination the mass is palpable, firm, and mobile, without any signs of erythema or induration; the patient nevertheless has decreased left hand grip strength and an abnormally positioned left upper extremity at rest. Laboratory evaluation results, including a complete blood cell count, a complete metabolic panel, and inflammatory markers, are normal. Radiography (Fig 1) and ultrasonography (Fig 2) are performed. Findings on initial examination are concerning for potential malignancy, so additional imaging is obtained to better define the mass. A magnetic resonance image (MRI) reveals a 4.6 × 4.2 × 5.1-cm, solid, peripherally enhancing, encapsulated mass with low vascularity in the left axilla (Fig 3). A positron emission tomographic/computed tomographic scan (PET/CT) shows enhancement localized only to the primary mass with a maximum standardized uptake value (SUV) of 4.7 (Fig 4). In PET/CT, SUVs are a quantitative measure of radioactivity level in a mass; responses to therapeutic interventions can also be measured in the same manner. The pediatric surgery service is consulted, but due

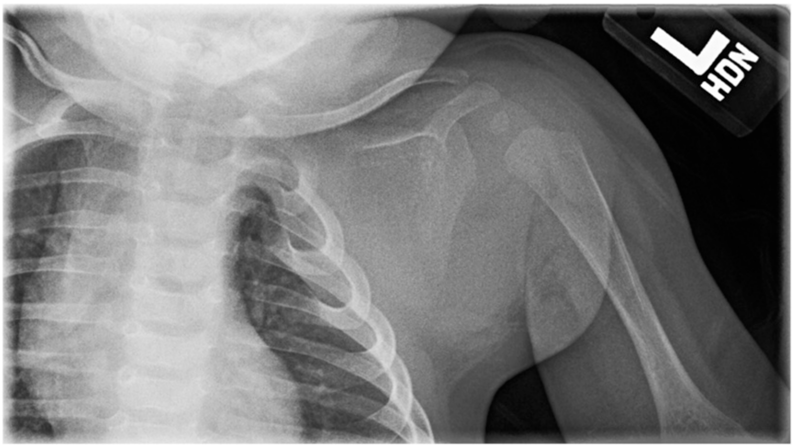

Figure 1. Radiograph of a 3-month-old boy with a localized palpable left shoulder mass. This is a left clavicle view demonstrating a soft tissue mass with ill-defined borders with mass effect to the left upper ribs.

AUTHOR DISCLOSURE Drs League-Pascual and Hartman have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

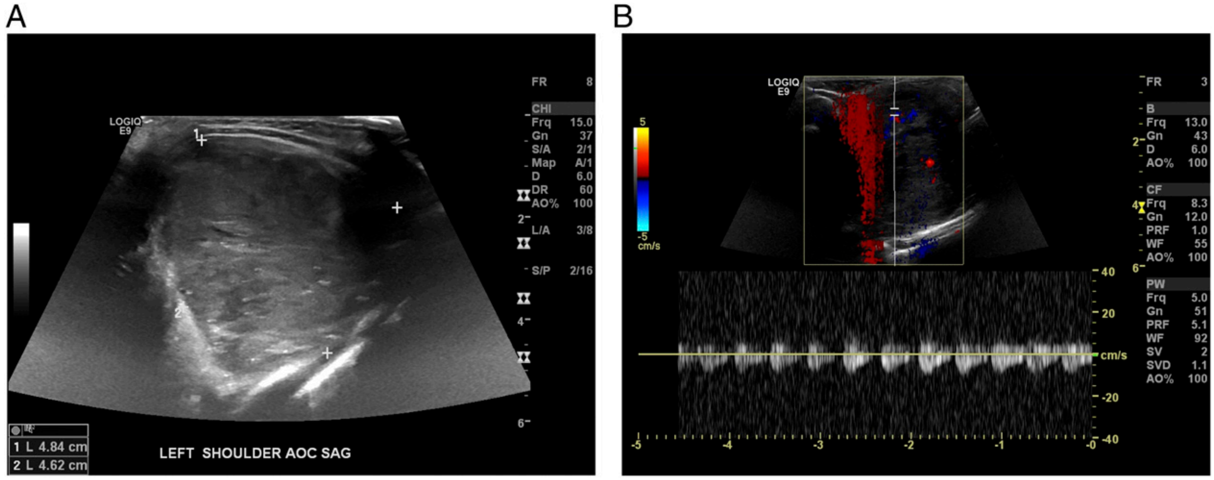

Figure 2. A, Targeted superficial ultrasonographic image of the anterolateral aspect of the left upper chest near the shoulder girdle in sagittal view. There is a large 4.8 × 4.6 × 5.0-cm, vascular, heterogeneous mass stemming from the underlying soft tissues. B, There are low resistance arterial waveforms, ruling out a vascular anomaly.

to the size and anatomical location of the mass, surgical resection is deferred. A core needle biopsy leads to the diagnosis.

Diagnosis

A diagnosis of an undifferentiated sarcoma is made, and appropriate chemotherapy is provided. After several cycles of chemotherapy, both MRI and PET/CT show an interval increase in size measuring 6.1 × 5.7 × 7.0 cm, with an increased SUV of 5.1 (Fig 5). The chemotherapy regimen is modified, although the mass continues to progress. On further pathological review the soft tissue sarcoma is characterized as a malignant rhabdoid tumor (MRT).

DISCUSSION

The incidence of either a benign or malignant soft tissue mass in an infant is not known. The differential is broad and depends on age and location. The most common masses in the infantile period are usually vascular. They can either be congenital vascular malformations or true neoplasms, which range from benign simple hemangioma to the more

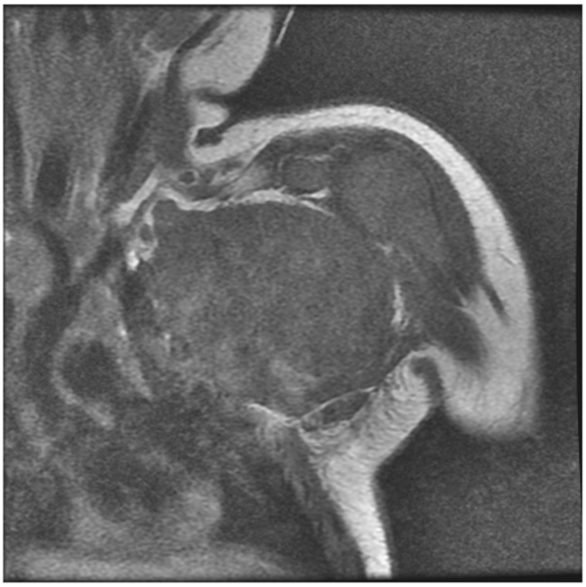

Figure 3. At the time of diagnosis, a T1-weighted coronal magnetic resonance image with contrast demonstrates a 4.6 (transverse) × 4.2 (craniocaudal) × 5.1-cm (anterior to posterior), large, solid, peripherally enhancing, encapsulated mass in the left axilla.

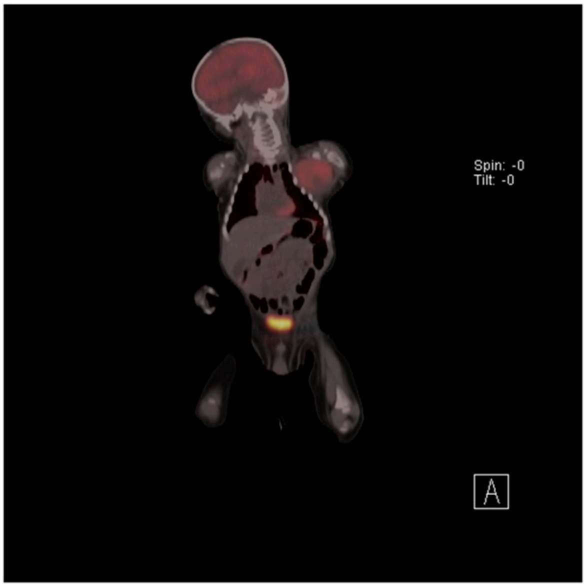

Figure 4. At the time of diagnosis, a positron emission tomographic/computed tomographic scan in coronal view shows hypermetabolic activity at a maximum standardized uptake value of 4.7.

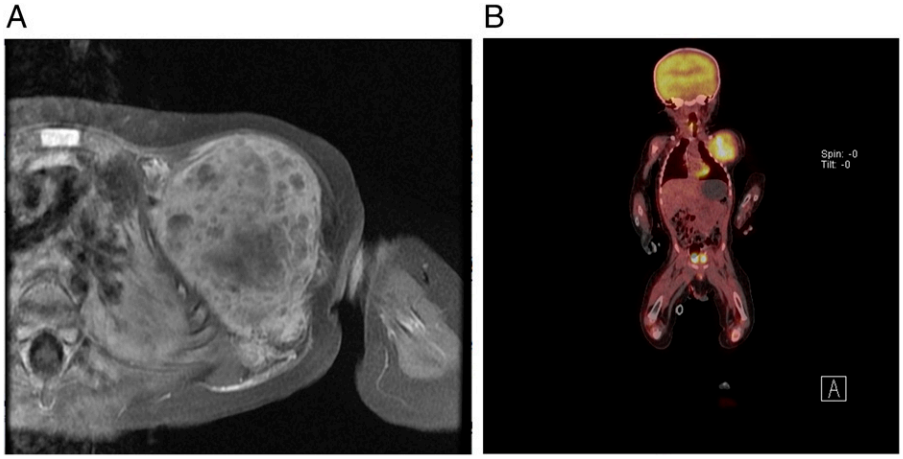

Figure 5. After several cycles of chemotherapy. A, T1-weighted axial magnetic resonance image with contrast demonstrates an interval increase in size at 6.1 (transverse) × 5.7 (craniocaudal) × 7.0 cm (anterior to posterior). B, Positron emission tomographic/computed tomographic scan in coronal view shows increased hypermetabolic activity at a maximum standardized uptake value of 5.1, with areas of necrosis.

locally aggressive Kaposi hemangioendothelioma. Nonvascular masses include soft tissue sarcomas (STSs); according to the Surveillance, Epidemiology, and End Results (SEER) database, in infants younger than 1 year, STS ranked fifth as the most prevalent malignancy in infants. Types of STS include rhabdomyosarcoma, infantile fibrosarcoma, and, in this case, MRT. Malignant rhabdoid tumor is a very rare and extremely aggressive cancer, with 5-year overall survival of 24%. (1) Malignant rhabdoid tumors most commonly develop in the kidneys but can develop in other sites of the body and are sometimes called extrarenal rhabdoid tumors, or in the central nervous system as atypical teratoid/rhabdoid tumors. They can be treated, but poor prognostic factors include young age (birth to <2 years), metastatic disease, and, based on the patient's age, the inability to use radiotherapy. Radiotherapy is a key component of treatment, but it is inherently detrimental to the long-term development of an infant. Its use is considered on a case-by-case basis. (2)

Diagnosing neonatal soft tissue tumors can be difficult and requires a multidisciplinary approach, including the integration of clinical, pathological, and radiologic features of the tumor. (1) No serum markers are available for the diagnosis of soft tissue sarcomas, and because the patient's initial radiograph is not able to differentiate whether the mass is benign or malignant, the diagnostic approach begins with imaging. (3) Ultrasonography with Doppler is the first-line imaging modality for a soft tissue mass because it prevents unnecessary radiation exposure to an infant during the diagnostic evaluation and is the preferred way to confirm whether any lesions are cystic or vascular in nature. Suspicion of a sarcomatous lesion should warrant further imaging with MRI and PET/CT. These images can further identify the anatomical extent of a mass, particularly if surgical intervention is needed, and whether there is any metastasis.

Histologically, this patient's tumor was initially reported as a sarcoma of uncertain differentiation and, therefore, was not specifically pathognomonic for MRT. Genetic analysis of this patient's tumor using whole exome sequencing nevertheless revealed a somatic mutation of the *SMARCB1* gene. Typically, MRTs have loss of heterozygosity of *SMARCB1*, a gene that drives tumorigenesis by epigenetic dysregulation. Mutations are frequently detected in the germline; our patient is the first to have a somatic mutation of its kind. Epigenetic targeted therapies for *SMARCB1* mutations based

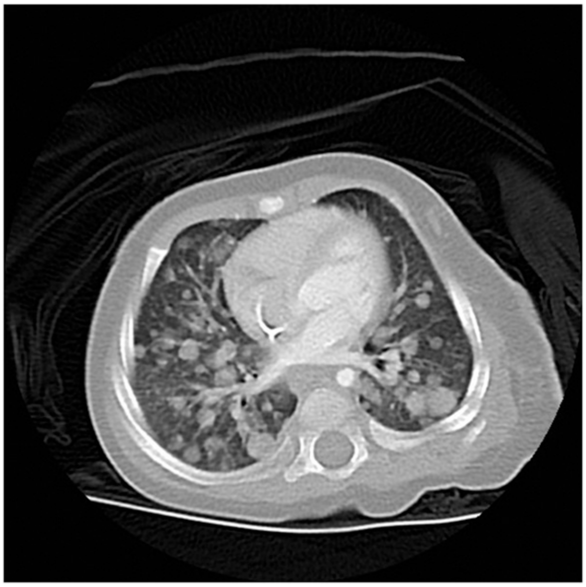

Figure 6. Chest computed tomographic scan in axial view displays multiple pulmonary nodules bilaterally consistent with metastatic disease.

on specific metabolic pathways have been developed and are currently in clinical trials. (4) Preclinical animal models show promising results in MRT response, and pediatric phase I/II clinical trials are currently under way for several of these agents.

Patient Course

The patient is taken to surgery, requiring a total left upper extremity amputation due to the extent of neurovascular involvement. Pathologic evaluation of the mass is consistent with MRT. A radiograph and chest CT scan subsequently revealed pulmonary metastasis, and the disease progressed rapidly (Fig 6). The patient died approximately 5 months after initial presentation.

Summary

- The differential diagnosis for a soft tissue mass in an infant is broad, although malignancy should always be suspected.
- Malignant rhabdoid tumor is a rare malignancy in an infant and has a dismal prognosis.
- Imaging plays a significant role in the diagnostic staging and risk classification process for these particular tumors, and in measuring response to treatment.
- Infants with MRT require a multidisciplinary approach that includes the pediatric oncologist, pediatric surgeon, pediatric radiologist, and pathologist.

Note. This case is based on a presentation by Dr James C. League-Pascual and Dr Kip R. Hartman at the 29th Annual Meeting of the American Society of Pediatric Hematology and Oncology, Minneapolis, MN, Author-Attended Poster Session B on May 13, 2016. Poster No. 794.

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Infection Control and Isolation Considerations for the Pediatric Practitioner

Munjal

Pediatric Intracranial Hypertension

Aylward, Reem

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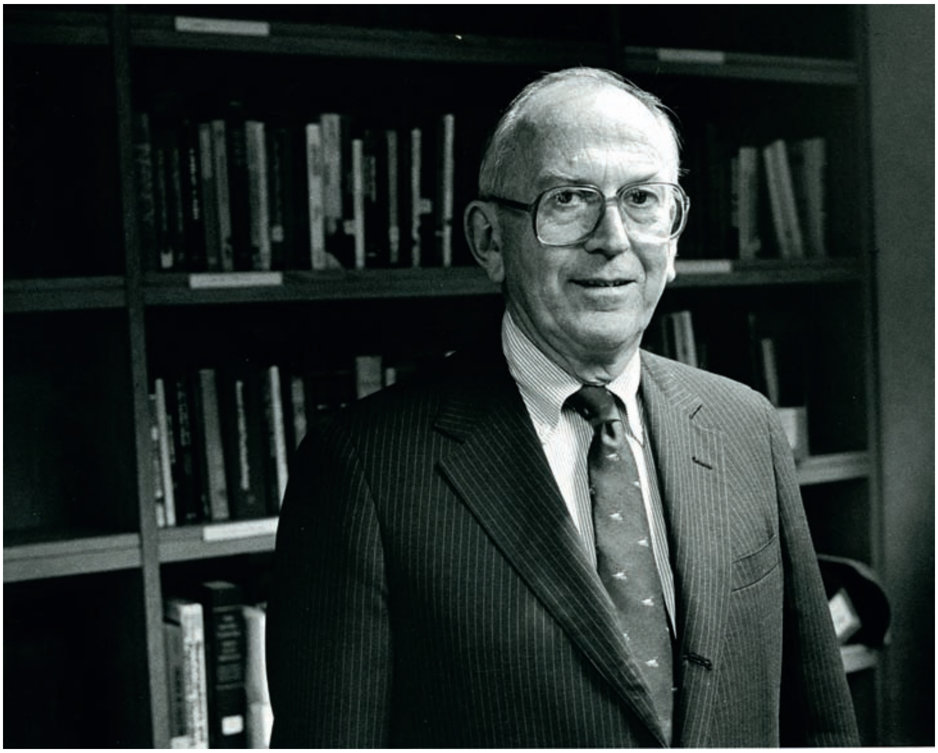
ONLINE

Visual Diagnosis: Recurrent Seizures and Concomitant Skin Changes in a 16-year-old Boy

Gupta, Talathi, Ventura, Prokhorov



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Commentary: pages 159-160

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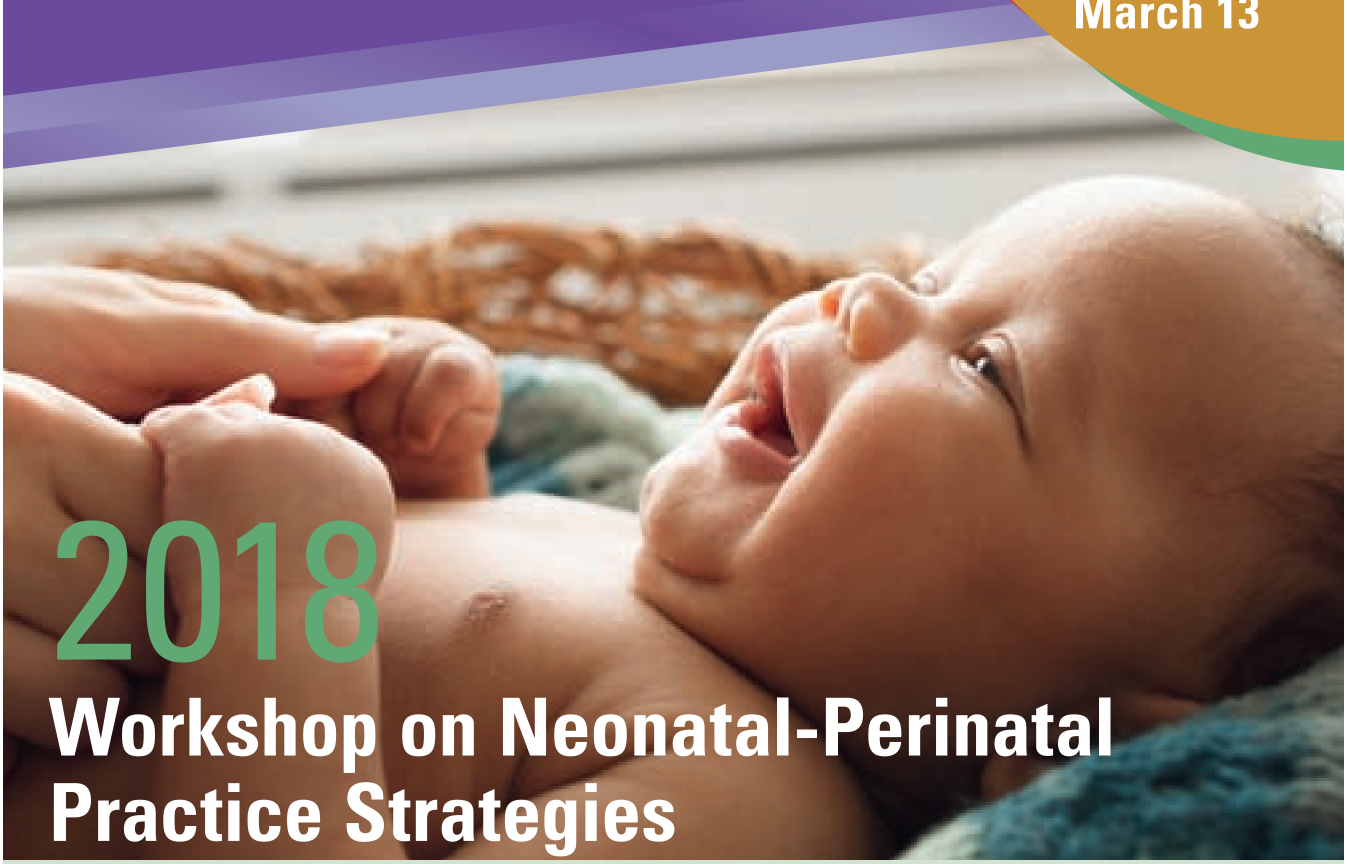

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Infection Control and Isolation Considerations for the Pediatric Practitioner

Iona Munjal, MD*

*Department of Pediatrics, Children's Hospital at Montefiore, Bronx, NY

Education Gap

With the increasing trend of transitioning acute care to outpatient care, pediatricians in the office setting should be aware of and adopt infection control measures.

Objectives

After completing this article, readers should be able to:

1. Provide evidence for providers working in all care delivery settings regarding the need for good infection control practices.
2. Define the differences in patient populations and aspects of care delivery that influence isolation practices for pediatric patients.
3. Define the different types of precautions used and emphasize the need for standard precautions, including effective hand hygiene, in all settings.
4. Differentiate between the isolation types based on transmission of the likely pathogen.
5. Identify specific infection control strategies to decrease health-care–associated infections.
6. Outline local, regional, and national strategies to decrease the burden of health-care–associated infections in pediatric patients, including new ideas that may change or contribute to the field in the coming years.

AUTHOR DISCLOSURE Dr. Munjal has disclosed that in addition to her appointment at Montefiore Medical center, she is now a full-time employee at Pfizer in vaccine research and development. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
HAI	health-care–associated infection
MDR	multidrug-resistant
PPE	personal protective equipment
RSV	respiratory syncytial virus

INTRODUCTION

Health-care–associated infections (HAIs) continue to represent a major burden to pediatric patients in the United States and are often preventable. (1)(2) It is estimated that 3% to 5% of children admitted to hospitals acquire an HAI, (3) which is associated with significant costs to the health-care system. (4) Infection preventionists have become a staple of acute care facilities, and their efforts have been shown to be cost-effective. (5) In the acute setting, this investment in infection prevention infrastructure is paying off. A significant reduction in central line–associated bloodstream infections was demonstrated between the last 2 major national surveys in 2008 and 2014. There have also been reductions in *Clostridium difficile* and methicillin-resistant *Staphyloccoccus aureus* HAIs in acute care hospitals. (6)

With the increasing trend to transition care from acute care to outpatient or chronic care settings, leadership in these areas is increasingly tasked with a variety of infection control issues. This is often coupled with a lack of shared and readily available infrastructure that has proved so beneficial in the inpatient arena. This places an increasing burden on individual pediatric providers to familiarize themselves with the application of infection prevention and control. Those with oversight of the patient care facility must ensure that they have sufficient human resources and a design layout that facilitates compliance with infection prevention and occupational health best practices.

THE CHANGING WORLD

In addition to the shifts in care location, less predictable external factors are challenging the way we approach isolation issues for infectious pathogens. These factors include the increase in global traffic and human urbanization. These factors bring all patients in closer proximity to emerging infectious pathogens not previously encountered in the United States. Just as severe acute respiratory syndrome coronavirus and pandemic influenza brought to light the need to have procedures in place to contain droplet and aerosolizing procedures, so have Ebola virus and Middle East respiratory syndrome coronavirus highlighted the importance of obtaining a travel history to determine a patient's isolation status. (7)(8)(9) Biocontainment units and comprehensive personal protective equipment (PPE) coverage have thus moved from the reels of Hollywood outbreak movies to Centers for Disease Control and Prevention (CDC) updates and national headlines. There is a disturbing trend away from immunizing children. In some ways, we can capitalize on these trends by taking the opportunity to address infection control issues with our patients and our staff. We can incorporate good practices such as cough etiquette and vaccination in a discussion of factors that we can control in what has become a less predictable infectious disease landscape.

Another factor that highlights a new reliance on infection control in practice involves the emergence of multidrug-resistant (MDR) organisms or bacteria and viruses for which treatment options are either very limited or nonexistent. Chief among these threats is the presence of carbapenem-resistant Enterobacteriaceae. These gram-negative bacteria have rapidly spread during the past 20 years, with isolates now found in 44 states. (10) Resistant to drugs of last resort, often these patients can be treated only with drugs such as colistin. The recent discovery of a colistin-resistant *Escherichia coli* harboring a plasmid-borne resistance gene, *mcr-1*, in May 2016 in a US patient with no recent travel indicates that through transmission of genetic material, pan-resistant bacteria are on the horizon. (11) It will take many years to develop newer antimicrobials against these resistant microbes, leaving prevention through isolation and safe hospital practices the sole weapon in our armamentarium.

PEDIATRIC CHALLENGES IN INFECTION CONTROL

It is important to note that there are factors that increase the likelihood of the transfer of infectious material during the routine care of pediatric patients that is not seen in other populations. Young children readily acquire and transmit infections. Aspects of care such as feeding, cuddling, changing, and playing require a level of close and sustained intimate contact. Anticipating the need for these practices should appropriately inform decisions around isolation and PPE. In addition, the constant presence of caregivers who provide meaningful support for the patient is encouraged, but those same caregivers may be the very ones who are at risk for acquiring or transmitting an infectious agent. Pediatric patients are known to be at higher risk for acquiring infections from the community while hospitalized. This may be due to the physical design of clinical spaces or to the presence of many visitors, including siblings and other children. It has long been a practice to build multibedded pediatric units such as NICUs or chronic care facilities. These present a daily challenge and are prone to experience outbreaks in an extremely vulnerable patient population.

There are also congregative pediatric policies designed to encourage social development that may complicate infection control, including kangaroo care in the neonatal units, parental rooming in, and the grouping of patients during in-hospital schooling or playroom activities. In both the inpatient and outpatient settings, toys and other objects that stimulate play are encouraged for comfort and stimulation but, when not properly cleaned and disinfected, pose a risk for transmission.

PATHOGEN TRANSMISSION

Prevention is the mainstay of infection control, and the proactive identification and containment of an infectious pathogen requires knowledge and preparedness. The isolation status of a patient is determined by the potential for transmission of an organism within its environment (Table 1). This requires access to knowledge about a suspected infectious agent and how it is transmitted for all staff, including greeters or nonmedical staff. The principal modes by which all infections can be spread are direct and indirect contact, droplet, and airborne transmission. (7) Direct contact involves the direct physical transfer of a microorganism between an infected or colonized person and a susceptible host. Examples include touching, kissing, or sexual contact. Transmission via indirect contact involves the spread of a pathogen through a colonized fomite, such as bedding, toys, utensils, biological products, or medical equipment (including catheters). Food and drinks can also represent vehicles through which infectious agents can pass. In both droplet and airborne transmission, infectious particles are propelled through the air. With droplet transmission, the particles are large (>20 μm), are relatively heavy, and fall to the ground after traveling only short distances (historically ≤ 3 feet). Patients standing within 3 to 6 feet risk direct deposition on their mucous membranes or skin. Subsequent entry to the respiratory tract can then occur. Airborne droplets, on the other hand, tend to be much smaller particles (approximately ≤ 5 μm). They are relatively light and can be suspended in air for extended periods or become more widely dispersed (eg, through ventilation systems) before contact with a host's mucous membranes. (7)(12) This is the basis for nosocomial transmission of tuberculosis (airborne transmission) around entire hospital wards, whereas pertussis (droplet transmission) typically affects those in the same room or clinical space.

STANDARD BEST PRACTICE = STANDARD PRECAUTIONS

All clinical providers should use the tiered system of standard precautions plus the addition of any transmission-based precautions as needed for certain infections. Standard precautions must be used consistently in all health-care settings regardless of the suspected or confirmed presence of an infectious agent to decrease the risk of transmission of pathogens to staff and other patients. (7)(13) Standard precautions include consistent hand hygiene, the use of PPE befitting the pathogen and exposure, maintaining a safe environment, and promoting good respiratory hygiene. Because clinical providers routinely encounter bodily fluids during the course of patient care, standard precautions are designed to protect against the acquisition of seen and unseen agents that may be present.

Hand hygiene is the single most important factor in reducing HAIs. (14) Despite the abundance of efficacy data, however, published compliance rates remain alarmingly low, and outbreaks due to transient flora transmission via the contaminated hands of health-care workers continue to be reported. (15) Factors that contribute to poor compliance include understaffing, high patient acuity, defective materials, structural design barriers, and education. Steps must be taken to address these challenges up front to ensure the best chance of success. For example, positioning easy access to sinks or full alcohol-based hand rub dispensers may be

TABLE 1. **Examples of Common Transmission-Based Precautions (12)**

CONTACT PRECAUTIONS	DROPLET PRECAUTIONS	AIRBORNE PRECAUTIONS
Clostridium difficile	Adenovirus	*Mycobacterium tuberculosis*
Enteroviruses	*Bordetella pertussis*	Measles
Hepatitis A	*Haemophilus influenza*	Varicella (with contact precautions)
Herpes simplex	Influenza	
Major, draining abscess	*Mycoplasma pneumoniae*	
Multidrug-resistant organisms[a]	*Neisseria meningitidis*	
Parainfluenza virus	Parvovirus B19	
Respiratory syncytial virus	Rhinovirus	
Staphyloccoccus aureus		
Salmonella		
Scabies		
Shigella		

[a] *Multidrug-resistant organisms are bacteria that have developed resistance to multiple classes of antibiotics.*

the first step to improved infection control practices in a facility.

Hand hygiene must be used before and after each patient contact and after removing any necessary PPE, including gloves. Hands should be washed with soap and (warm or cold) water for 20 seconds while paying special attention to frequently missed areas, including the backs of the hands, the spaces between the fingers, the fingertips, and under the nails. Soap and water is preferred in cases in which the hands are visibly soiled or in which exposure to a spore-forming organism is suspected (*C difficile* being the most common). In many infection control programs, proper hand hygiene also includes restricting those in high-risk health-care settings from keeping nails long or wearing artificial nails because they have been associated with outbreaks of gram-negative bacillus and candidal infections. (7)

Waterless sanitizers with at least 60% alcohol can be used when hands are not visibly dirty or greasy and the removal of harmful drugs or chemicals is not a concern. Alcohol-based hand rubs cannot be used when certain agents, particularly diarrhea-causing *C difficile,* norovirus, and C*ryptosporidium,* are being considered. Different alcohol-based hand rub delivery systems, including foams, gels, and wipes, have equal efficacy in the context of a clinical trial, (16) but products that require a prolonged dry time may lead to reduced amounts used and thus reduced efficacy. (17) Standard dispensers that administer the appropriate amount are advised. Alcohol-based products vary, but most require approximately 3 mL of product rubbed on the hands for approximately 30 seconds, or until the recommended amount of product evaporates, and the hands are completely dry. (18) As with soap and water, attention must be given to the backs of the hands using a hand over hand technique, the spaces between the fingers, the tips of the fingers, and under the nails.

Studies have shown improved compliance by switching from handwashing to the use of an alcohol-based hand antiseptic. (19) Therefore, alcohol-based hand antiseptics should be emphasized where compliance is low, particularly when easy access to a handwashing station is limited. Alcohol-based products can cause cracking or drying of the skin. Lotions should be readily available because they may increase skin hydration and aid the normal lipid barrier and increase compliance with hand hygiene. (20)

PROTECTIVE PERSONAL EQUIPMENT

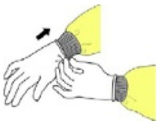
Gloves, isolation gowns, protective eye equipment, and other personal gear are important components of PPE (Tables 2 and 3). In addition to reducing patient-to-patient spread, they are mandated by the Occupational Safety and Health Administration Bloodborne Pathogens Standard for the protection of providers. (21) As the medical community collectively learned in the Ebola virus epidemic, the proper technique for putting on (donning) and taking off (doffing) PPE is as important as the specific equipment used in protecting against occupational pathogens. (22)

Gloves should be worn when coming into contact with body fluids and potentially hazardous infectious material. (7) Under standard precautions, this applies to any anticipated contact with blood and all body fluids, secretions, and excretions (except sweat); nonintact skin; and mucous membranes. Tasks should be performed that go from clean to dirty body sites to prevent cross-contamination, and gloves should be changed if they are used in areas of high infectivity (eg, a purulent dressing change). While using gloves, it is critical to avoid touching one's own face or adjusting glasses, hair, or masks. Gloves should be removed or changed during a patient encounter if a handheld or electronic device is used. Gloves are always single use and immediately should be disposed of after removal. It is important to then immediately perform hand hygiene even if a new set of gloves is to be worn because hands may have become contaminated during glove removal. Small perforations may also be present in gloves, particularly those worn for extended periods.

Isolation gowns should be used during procedures or patient care activities in which a provider's exposed skin and/or clothing is anticipated to come into contact with blood, body fluids, secretions, or excretions. (7) Gowns should be made of an impervious material that prevents contamination of skin or clothing. When needed, gowns should be the first piece of PPE to be put on before entering a patient's room and should be removed before exiting. Care must be taken to avoid skin gaps, particularly around the wrist area, and gowns should be secured at the neck and waist to prevent slippage during care.

Masks should routinely be worn to protect the mouth and nose when a procedure is likely to spray or splash fluids (such as endotracheal suctioning). Masks should also be worn to protect patients during procedures in which oral or nasal secretions could contaminate a sterile field (eg, during a dressing change for a central line). Finally, patients who are coughing and have the potential to disseminate respiratory secretions should also wear masks, particularly when traveling within a facility or in common areas. The additional use of eye shields, goggles, or full-cover PPE should be considered in select circumstances where exposure to those areas is anticipated. (7)

TABLE 2. Recommendations for the Application of Precautions for the Care of Patients on Standard and Enhanced Precautions (7)

COMPONENT[a]	TECHNIQUE	INDICATED
Soap and water	Wash hands for 20 seconds. Sinks should be conveniently placed and free of clutter.	Before and after each patient contact and after doffing gloves or PPE Preferred over alcohol-based hand sanitizer in the following circumstances: When hands are visibly soiled Required with *Clostridium difficile*, norovirus, *Cryptosporidium*, or *Bacillus anthracis* Before eating After using the restroom
Alcohol-based hand sanitizer (must contain ≥60% alcohol)	Apply the product to the palm of one hand as per the label instructions. Rub hands together until the product is completely dry.	When soap and water is not required
Gloves 	Make sure that gloves are pulled on all the way and cover the forearm or sleeves. Remove before other PPE by grasping the exterior of the glove with the other hand. Pull off the glove with the contaminated exterior folded on the inside. Holding the contaminated glove in the gloved hand, slide a finger from the ungloved hand under the wristband of the remaining glove. Gently pull off the glove so that it is also inside out, forming a bag for the other glove, and discard the pair. Wash hands after removal.	Required for contact with blood, body fluids, mucous membranes, nonintact skin, and contaminated items
Surgical or procedure mask 	Masks should be applied before donning gloves. Make sure that the front fully covers the nose and mouth snuggly, then secure it to the head with ties or elastic. The front of the mask should be considered contaminated. The mask should be removed from behind after all other PPE to prevent mucous membrane exposure during the doffing process.	During procedures likely to generate splashes or sprays of blood or body fluids Required within 3–6 feet of patients with infections proved to be transmitted via large respiratory droplets to protect mouth and nose
N95 respirator mask (round or trifold)[b] 	They require annual fit testing to ensure that the provider can get a good seal. Place on the face and apply the top strap at the crown of the head and bottom at the base of the neck. Straps should not be crossed. Ensure that it is sealed with a seal check before use. The mask should be removed from behind with the bottom strap released first. The mask is removed after all other PPE to prevent mucous membrane exposure during the doffing process.	During aerosol-generating procedures or on patients with infections proved to be transmitted by respiratory aerosols
Eye protection 	These can be found either attached to a surgical mask or separately in the form of goggles or safety glasses. They should be placed snug on the face. They should be removed by the straps because the front should be considered contaminated.	Required during procedures likely to generate splashes or sprays of blood or body fluids into the eyes

Continued

TABLE 2. **(Continued)**

COMPONENT[a]	TECHNIQUE	INDICATED
Face shield 	The face shield should cover the forehead, extend below the chin, and wrap around the side of the face.	Required during procedures likely to generate splashes or sprays of blood or body fluids When skin protection, in addition to mouth, nose, and eye protection, is needed or desired, eg, when irrigating a wound or suctioning copious secretions
Surgical gown 	If worn, it should be put on as the first piece of PPE. You must secure the upper portion at the neck and lower portion using simple bows. To remove, unfasten the bows and roll down away from the body with the clean side facing out in a bundle.	Protect skin and/or clothing from contact with blood or bodily fluids Used with patients on contact precautions

PPE=personal protective equipment.

[a] *The pictures are from CDC Guidance for the Selection and Use of PPE in Healthcare Settings (https://www.cdc.gov/HAI/prevent/ppe.html).*

[b] *More N95 respirator examples can be found at https://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/respsource3healthcare.html#e.*

Other equipment, including eye goggles or face shields, must be considered during certain patient tasks or with certain pathogens. Aerosol-generating procedures (ie, bronchoscopy) can propel larger droplets farther and can impact all mucous membranes. If an area is very soiled or a procedure results in exposure below the waist (ie, during deliveries), shoe or shoe and leg coverings should be used.

SAFE ENVIRONMENTS

Standard precautions also govern the use of safe injection practices, the proper handling or disposal of items contaminated with infectious body fluids, and keeping a clean patient environment. This includes the use of sterile, single-use disposable needles and syringes for each injection. (23) After use, needles should not be recapped and should be placed into a designated, puncture-resistant container. Reusable equipment is not to be used for the care of another patient until it has been appropriately cleaned and reprocessed, and single-use items must be discarded. This includes all small, frequently used items such as stethoscopes and blood pressure cuffs and larger, more problematic items such as endoscopes that must be cleaned between patients by dedicated, trained staff. (24) Patient care and waiting areas should be properly cleaned and disinfected. High-touch reusable equipment should be wiped down at least daily and more often if visibly soiled or comes into contact with a potentially infected patient. During environmental disinfection, special attention should be given to high-touch surfaces, including doorknobs, bed rails, and examination tables. Items less commonly encountered by patients (ie, computers, keyboards, etc) should still be cleaned and disinfected regularly, particularly if shared among staff members.

OPERATIONALIZING INFECTION CONTROL

The modern shift away from acute care increases the likelihood that well patients, even those who are immunosuppressed, are integrated into outpatient practices alongside patients who may be contagious. A plan should be established for the triage and placement of patients at all points of entry within a facility to screen for those at increased risk for transmission. This can include signage and general questions regarding fever, rash, travel, and acute illness. Patients thought to be infectious can then be advised to wear a surgical mask and be offered tissues and hand sanitizer. When available, they can be prioritized into designated isolation areas that do not exhaust circulating air into common areas. Isolation rooms that are most functional contain a covered commode and emesis bags in addition to externally placed PPE supplies that allow the provider space to properly don them before entry. When isolation areas are not available, and respiratory pathogens are a concern, patients can be instructed on cough etiquette (covering their nose and mouth when coughing or sneezing), to wear a surgical mask, and to be spatially separated as much as is feasible (optimally 6 feet). Patients who are at increased risk of acquiring infection (eg, immunocompromised patients or unvaccinated newborns and others) should also be

TABLE 3. **Requirements for Standard and Transmission-Based Precautions (12)**

	STANDARD	CONTACT TRANSMISSION	DROPLET TRANSMISSION	AIRBORNE TRANSMISSION
Single-patient room	No	Yes[a]	Yes[a]	Yes, negative pressure ventilation[b]
Door closed	No	No	Yes	Yes
Dedicated durable medical equipment (eg, blood pressure cuff)	No	Yes	Yes	No
Gloves	No[c]	Yes	No	No
Gowns	No[c]	Yes	No	No
Masks	No[c]	No	Yes	Yes

[a] *May be a cohort of patients with the same pathogen.*
[b] *Also called* airborne infection isolation room.
[c] *Additional precautions are to be applied in any setting as needed.*

identified and scheduled for visits in a manner that decreases their exposure. Separate waiting areas for sick and well children can also be considered.

Before use in patient care facilities, the type of high-touch toys or play surfaces should be carefully considered. Only washable, nonabsorbent toys should be placed in common play areas. Because children may place toys in their mouths, they should be not only routinely disinfected but also rinsed with water (at least weekly). (25)(26) Toys that are composed of fabric or fur can be given to individual patients for single use. These carry higher amounts of coliforms and cannot be adequately disinfected. A toy wash bin can be provided to facilitate the separation of clean and dirty items.

TRANSMISSION-BASED PRECAUTIONS

Transmission-based precautions add a level of enhanced protection beyond standard precautions through the use of PPE. They are to be performed with patients who are known or suspected to be infected with or colonized with epidemiologically important infectious agents that are easily spread. These precautions decrease rates of transmission within and around facilities and complement good environmental programs and disinfection. (27) They also provide protection for the provider by decreasing the risk of person-to-person transmission. Optimally, health-care workers caring for patients who require isolation should receive comprehensive training and demonstrate competency in performing infection control procedures.

Transmission-based precautions must often be initiated empirically based on certain clinical syndromes or conditions. Most pathogens are spread via a preferred route based on common patient presenting symptoms, but some infectious agents can be transmitted by more than 1 route, depending on the symptoms (eg, adenovirus). Enhanced use of PPE up front is, therefore, preferred during an initial evaluation, and modifications in isolation can be made once a diagnosis is known. Signage and a partnership with patients to encourage self-identification of infectious agents will help enhance the efforts of staff.

Contact precautions apply to patients who are incontinent of stool or have draining wounds, uncontrolled secretions, or draining ostomy tubes or catheters. In this precaution category, gloves and gowns are not only recommended but also required during all contact with a patient's environment. Patients should be kept in single rooms or at a distance of greater than 3 feet in a multipatient space with a dedicated commode to reduce the opportunity for fomites to pass between patients. Durable medical equipment must be sanitized between patients.

Contact precautions are indicated for patients infected or colonized with MDR bacteria, including methicillin-resistant *S aureus*, vancomycin-resistant enterococcus, and MDR gram-negative bacilli. Other indications include pathogens transmitted via the fecal-oral route. Children with respiratory syncytial virus (RSV), parainfluenza, or enterovirus should also be placed under contact precautions. Due to the resistance to alcohol-based hand rubs and their tendency to cause institutional outbreaks when disinfection practices are not in place, extra precautions should be considered empirically for the presentation of diarrheal disease until *C difficile* and norovirus are ruled out. (7)(28)

Droplet precautions require the use of a mask before room entry in addition to standard precautions. Although spread to mucous membranes is a concern within 3 to 6 feet, the droplets are not suspended in air and, therefore, do not require special ventilation systems or fine particle masks unless an aerosol-generating procedure is performed. Single-patient rooms are again preferred. If cohorting of patients with the same respiratory pathogen is needed for space considerations, a distance of 3 to 6 feet must be maintained between patients, with a curtain drawn at all times. Patients traveling within a facility where they may come into contact with others should wear a surgical mask themselves.

Because many respiratory infections are not identified, and bronchiolitis and viral pneumonia may be triggered by etiologies that are spread by either droplet (adenovirus, influenza, etc) or contact (RSV, parainfluenza virus, etc) precautions, combined contact plus droplet precautions can be considered for upper respiratory tract pathogens that are unidentified. Pathogen-specific precautions may be modified when an etiology is determined, although codetection of multiple respiratory pathogens transmitted via different routes (eg, influenza by droplet and human metapneumovirus by contact) is not uncommon. (29)

Airborne isolation requires protection against droplet nuclei by the addition of a respirator and a designated airborne isolation room. An appropriate respirator is one that filters 1-μm particles with 95% efficiency (ie, an N95 mask). For infectious particulate matter, there is no advantage of one product over the other as long as they are approved by the National Institute for Occupational Safety and Health. (30) If nasal skin breakdown occurs, the trifold N95 masks may be preferred. A powered air-purifying respirator with a hood, as used with full impermeable suits by some Ebola virus and chemical hazard ready teams, can be considered for improved comfort and airflow if it is anticipated that care will have to be continuously delivered for prolonged periods or exposure will be high. However, powered air-purifying respirators must be charged, and the unit must be cleaned and disinfected, including changing filters according to the manufacturer's instructions. (22)

Patients with concern for airborne isolation should be placed in rooms that can accommodate the airflow required to clear fine particle agents. These negative pressure airborne isolation rooms should perform a minimum of 6, but preferably 12, air changes per hour. Their room's door must remain closed at all times. If unable to accommodate patients in a room with a high number of air exchanges, place a surgical mask on the patient before he or she is placed into an unoccupied room. The room should be left vacant for enough time to allow the probability of acquiring tuberculosis through low-volume exchange to decrease. In a typical medical office, there are typically 4 to 6 air changes per hour. Because, the number of droplet nuclei in that setting will be reduced by 99% in 49 to 69 minutes, leaving the room unused for at least an hour should be sufficient to prevent almost all cases of airborne transmission. (31) People with proven immunity to varicella or measles do not have to wear a mask to protect against those conditions even though airborne isolation is used for susceptible personnel.

Transmission-based precautions remain in effect for most diseases for limited periods until the natural course of the infection has concluded (eg, 7 days for influenza or for the duration of illness with disease due to parainfluenza virus). If the organism is highly susceptible to antimicrobial therapy (eg, meningococcal meningitis or group A *streptococcus*), 24 hours after initiation of appropriate treatment is the typical duration of isolation. When contact isolation is used for many MDR pathogens, they may remain in place for prolonged periods, until the patient leaves the facility or is proved to no longer be colonized. This can be modified on the advice of local and regional authorities. Patients may continue to shed MDR pathogens even when not symptomatic, and decolonization regimens remain unproved.

Common pathogens and their typical routes of transmission and isolation status are listed in Table 1. Certain pathogens merit particular mention, either by their infectivity or the frequency with which they are encountered in the pediatric domain. For example, although influenza virus is commonly spread via the droplet route, it has the capacity to remain suspended in air, and N95 masks are required for aerosolizing procedures. (32) Influenza is known to survive on environmental surfaces for extended periods and to be spread by direct and indirect contact. (33) Patients who present with an influenzalike illness can either have an alternate diagnosis or be co-infected with a virus spread via the contact route (eg, metapneumovirus). Owing to all these factors, some settings opt to use both droplet and contact precautions for individuals with symptoms consistent with influenza to greatly reduce propagation throughout the health-care setting.

Respiratory syncytial virus was found to be spread via the contact route in a study that found that volunteers acquired RSV when directly exposed to infected infants or indirectly exposed to contaminated surfaces but not at a distance of 6 feet. (34) Since then, contact precautions have been effectively used to prevent health-care transmission. However, RSV easily propagates around patient care settings even among providers who have measurable immunity. Therefore, some institutions have added masks and/or eyewear to prevent the risk of hand to mouth or eye contact in the close care required in a pediatric population, particularly in outbreak scenarios. (35)(36) There is some evidence of aerosolized RSV particles, but nosocomial spread via this route is not proved. (37)

C difficile and norovirus, although both spread via contact transmission, should be thought of as distinct in this category. They require soap and water for hand hygiene due to their resistance to alcohol. They are also difficult to eradicate from the environment and are quickly spread over high-touch surfaces. The patient care area should be disinfected with bleach-containing products, and dedicated equipment should be used for each patient. Therefore, in our institution, these 2 pathogens are differentiated from others in the contact isolation category as being *Contact "Plus."*

Other modes of transmission, including those via a vectorborne route and a vehicle route (ie, blood products), should be considered but would typically not affect isolation precautions from casual contact. This is true for diseases such as Zika virus disease and dengue. It is important, however, to identify other potential causes for diseases that may present in a similar manner (ie, meningococcal disease) that do require isolation and prompt evaluation.

PRECAUTIONS FOR VISITORS

When caregivers or other visitors accompany patients, questions regarding isolation of those persons must also be considered. This is important both for the protection of the caregiver and for the potential need to shield the patient or the facility from any infectious pathogens that the visitor may be incubating. Due to the anticipated limited movement of the caregiver among other patients, the likelihood that the caregiver and the patient have had sustained contact before the visit, and the difficulty in educating about and enforcing PPE use, most facilities do not use isolation precautions of any kind among visitors. The Society for Healthcare Epidemiology of America has supported this approach for visitors with "extensive documented exposure to the symptomatic patient prior to hospitalization." (38) However, there is likely a role for doing "just-in-time" training and using isolation for caretaker/patient dyads in which either the caregiver has not been exposed to the patient's suspected pathogen or for cases in which limiting spread of the pathogen is in the interest of public health. For example, contact precautions are advised for visitors to patients with extensively drug-resistant organisms, including carbapenem-resistant Enterobacteriaceae. Using contact precautions for visitors should also be considered for enteric pathogens, including norovirus, which have a high likelihood of causing illness in caregivers. (38) This is also pertinent in outbreak scenarios or in the case of a highly infectious emerging infectious disease, such as was the case with Ebola. Practically speaking in pediatrics, however, the prolonged care provided to most pediatric patients by their caregivers makes the use of PPE for inpatient or long-term care facility visitors impractical. It may be appropriate to suspend the use of PPE in these scenarios after a discussion with the families of the risk of the suspected pathogen. However, there continues to be a role for hand hygiene education and information regarding how the infectious disease is transmitted even if visitor PPE is not used. Visitors who are entering isolation rooms should also have limited movement to other parts of the health-care facility. (9)

Screening of visitors for communicable diseases should be part of a larger visitation policy that can balance family-centered care with infection control guidance. Visitors with active infections or a recent exposure to a communicable disease should be restricted. This may include but is not limited to fever, upper respiratory tract infections, rash, acute gastroenteritis, sore throat, flulike illness, or a history of oral polio vaccine receipt within the previous 3 to 6 weeks. Signage educating visitors on cough etiquette helps prevent the propagation of respiratory pathogens. Younger children may need to be screened or restricted, even if they are asymptomatic, because they frequently harbor and shed upper respiratory tract infections and may have difficulty containing their secretions. This is particularly true when circulating respiratory pathogens are at their peak. Furthermore, young patients should be discouraged from visiting rooms where another patient requires isolation for transmission-based precautions because these young visiting patients may not be able to reliably comply with hand hygiene and other practices to protect themselves.

OUTBREAKS, EXPOSURES, AND REPORTING

Providers in all care delivery environments must also be versed in policies around outbreaks and family notification of a communicable disease exposure when proactive measures fail to capture and isolate patients with active infections. Most outbreaks occur when standard precautions lapse. Whereas HAIs more broadly indicate infections acquired in any health-care delivery environment, nosocomial infections typically refer to those that are acquired in the inpatient setting, including those that appear after discharge and those that are acquired by staff.

For the purposes of tracking and reporting nosocomial infections through the National Healthcare Safety Network to the CDC, a nosocomial infection must *not* be incubating or present at the time of hospitalization, defined as the first 48 hours after admission. Depending on specific local, state, or national legislation, nosocomial infections may have to be reported through the National Healthcare Safety Network or other means. Physicians must be aware of the rules and regulations in their municipality, and policies and procedures for communication should be established with local and state health authorities regarding reportable diseases and suspected outbreaks. Tracking of all HAIs can also help serve as a surrogate measure of compliance to isolation measures.

When a breach in good isolation practices has occurred, exposed parties should be identified and notified based on the transmission capabilities of the proven infection, the susceptibility of the person to acquiring it, and the method of exposure. For some infections, there is available postexposure prophylaxis (ie, vaccination or varicella zoster immune globulin [human] [VARIZIG; Aptevo BioTherapeutics LLC, Berwyn, PA] for certain high-risk patients exposed to varicella) (39) that will significantly decrease the acquisition or severity of a disease and should be promptly considered. For others, postexposure prophylaxis is either not warranted or not available. Communication with patients and public health entities is important given that exposed patients may seek further care during the period of infectivity and place others at risk.

OCCUPATIONAL HEALTH

Occupational health is an important component of infection prevention and control and limits the spread of nosocomial transmission. It is virtually impossible to protect all susceptible individuals from certain infections such as varicella, measles, and influenza by avoidance alone because these diseases are highly communicable. Transmission overall is greatly reduced in the setting of a highly vaccinated population. Every health-care facility should have clear guidance regarding employee vaccination. Employee vaccination programs significantly reduce absenteeism and are associated with lower rates of disease-associated complications. (40)(41)(42) Programs that are the most successful at reaching full compliance in employee vaccination are those that use mandates. Other strategies, such as compliance training for those who refuse, are also successful.

Policies around the management of work exposures and work restrictions for those who are infectious should also be clear. Steps should be taken to eliminate all barriers to postexposure care for personnel. For example, postexposure prophylaxis against human immunodeficiency virus after occupation exposure should ideally be started within 2 hours of the event. (43) Many large institutions should and do keep postexposure prophylaxis packets on hand, and smaller facilities should know how to access medication and testing for workers in a timely manner.

PERSONNEL ATTIRE

Horizontal transmission of HAIs has been thought to involve not only the hands but also the attire of health-care workers. For the past several years, the National Health Service in the United Kingdom has mandated a “bare below the elbows” campaign in patient care to ensure optimal hand hygiene. Providers are required to wear short sleeves or long sleeves that are rolled up, and wristwatches, jewelry, and ties are prohibited. Although there is a good rationale for this practice, the Society for Healthcare Epidemiology of America has stated that there is insufficient evidence to support mandating such an approach because the effect on HAIs is unknown. There are several studies that report the presence of pathogenic bacteria on neckties: white coats and ties should be secured and white coats removed before contact with the patient’s environment to prevent patient-to-patient transfer of pathogens. Providers who opt to use white coats should launder them at least weekly and whenever they are contaminated or visibly soiled. (44)

PARTNERSHIPS AND RESOURCES

Not only government entities but also third-party payers and patients themselves are increasingly demanding reductions in medical care complications, including HAIs. Good isolation practices are a vital part of a multipronged approach to achieving the desired elimination of HAIs (ie, getting to zero). In this effort, building bridges to local, regional, and national partners is key. Not only can shared resources enhance individual compliance, but a reduction in transmission of pathogens at any one site affects the global health-care community. Infectious diseases gain access beyond hospital walls, and having the support of nearby epidemiology data and assistance is vital. Knowing, for example, the local incidence of methicillin-resistant *S aureus* or data regarding vaccine compliance to measles in your area helps to inform a practice from isolation to antimicrobial selection to disease identification. There are many national initiatives and educational tools to rely on (Table 4). In June 2015, the US Department of Health and Human Services announced that there are 9 health departments and associated hospitals in a national network of 46 other treatment centers that will become ongoing public and private partners to provide care to patients with severe, highly infectious diseases. These centers will enhance the nation's response to outbreaks on a global scale.

Other approaches, including preventing or replacing colonization of patients with MDR organisms should also be integrated into a holistic infection control program. Perturbations in bacterial flora are seen more in the most critical patients, (45) in whom isolation practices are the most challenging to maintain given the high care demands. Restoring high-risk patients to their normal microbiome may be more effective in the prevention of MDR organism HAIs than the use of antimicrobial prophylaxis or contact precautions.

Steps are also being taken to reduce unnecessary antimicrobials to minimize the emergence of MDR organisms through antimicrobial stewardship programs. In 2015, the White House released a National Action Plan for Combating Antibiotic-Resistant Bacteria to emphasize the importance of antimicrobial stewardship in complementing a good infection control program. One pathogen targeted for improvement is the reduction in antibiotic-associated *C difficile*. In pediatrics, both care and prescribing of antibiotics are primarily in the outpatient arena. More than 70% of pediatric *C difficile* infections occur in children in the general community, with most having recently taken antibiotics prescribed in a physician's office. (46) Reducing unnecessary administration of antibiotics for viral upper respiratory tract infections is one step that all physicians can take to decrease the need for isolation due to *C difficile*.

Universal adherence to best infection control practices remains low, and direct observation and feedback, considered the gold standard in observing compliance, can be costly and result in a Hawthorne effect (observer effect). The ability of a provider to follow best practices may compete with multiple patients who may have urgent care needs. New tools are needed given all the challenges around complying with hand hygiene, environmental, and isolation practices. Electronic hand hygiene dispensing counters, radiofrequency identification of compliance, alcohol vapor detection sensors, and video surveillance are among the many automated processes that are being trialed to improve hand hygiene rates. Hospitals are increasingly adopting UV lighting to enhance traditional cleaning, with a notable reduction in rates of pathogenic bacteria. Low-budget solutions exist too: wall-mounted alcohol dispensers should be installed in easy-to-reach locations in all practice settings, and physicians themselves can carry around portable containers of waterless agents. For providers who simultaneously care for multiple patients, compliance decreases as more patients are placed into isolation, with approximately 40% of a patient load as the "tipping point." (47) Nursing and other staffing assignments should be aware of

TABLE 4. **Resources for Infection Control Guidance**

Centers for Disease Control and Prevention
Clean Hands Count campaign: http://www.cdc.gov/handhygiene/providers/index.html
Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings: http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf
Guide to infection prevention for outpatient settings: http://www.cdc.gov/hai/pdfs/guidelines/Ambulatory-Care+Checklist_508_11_2015.pdf
Guideline for disinfection and sterilization in health-care facilities: http://www.cdc.gov/hicpac/pdf/guidelines/disinfection_nov_2008.pdf
Guidance on public reporting of healthcare-associated infections: recommendations of the Healthcare Infection Control Practice Committee: http://www.cdc.gov/hicpac/pdf/PublicReportingGuide.pdf
Occupational guidance
Guideline for infection control in healthcare personnel: http://www.cdc.gov/hicpac/pdf/InfectControl98
Vaccines for healthcare workers: http://www.cdc.gov/vaccines/adults/rec-vac/hcw.html
CDC Safe Injection Practices Coalition One and Only campaign: http://www.oneandonlycampaign.org
Occupational Safety and Health Administration bloodborne pathogens and needlestick prevention: http://www.osha.gove/SLT/bloodbornepathogens/index.html
HIV prophylaxis after occupational exposure: https://www.hivguidelines.org/pep-for-hiv-prevention/occupational/
Other
Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book*: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
Munoz-Price LS, Banach DB, Bearman G, et al. Isolation precautions for visitors. *Infect Control Hosp Epidemiol*. 2015;36(7):747–758.
National Action Plan for Combating Antibiotic-Resistant Bacteria, 2015: https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

CDC=Centers for Disease Control and Prevention; HIV=human immunodeficiency virus.

this limitation compliance and adjust workloads of caregivers accordingly.

The intimacy of pediatric care and the high rates of circulating respiratory pathogens in this population necessitate that meticulous hand hygiene and appropriate attention to standard isolation precautions occur during every patient contact event. Health-care facilities should continue to be places where patients can seek care without the fear of contracting infectious diseases. To do this, providers must enhance their knowledge, preparedness, and ability to track adherence to infection control practices. Work environments should be conducive to compliance, and education should be ongoing to reinforce the importance of practicing standard precautions on every patient.

Summary

- Dedicating staff and resources to infection prevention and control decreases rates of health-care–associated infections (HAIs) and reduces health-care–associated costs (evidence quality B). (5)
- Adherence to hand hygiene is the single most important factor in reducing HAIs, including the preferential use of alcohol-based hand rub for routine antisepsis and soap and water in instances when hands are visibly dirty, soiled, or with certain pathogens, including *Clostridium difficile* (evidence quality A). (14)
- Certain employee policies can affect rates of HAIs, including limitations on artificial nails (evidence quality A) (7) and mandated vaccination programs (evidence quality B). (40)(41)(42)
- Personal protective equipment, including gowns, gloves, and masks, should be used as part of standard precautions for patient interactions that involve contact with blood or body fluids (evidence quality B).
- In addition to standard precautions, strong evidence indicates that transmission-based precautions should be used for patients with suspected or documented clinically important pathogens (evidence quality A).
- Based on expert opinion supported by some observational studies, patients should be identified for isolation through systems that detect and manage potentially infectious persons at the point of entry for a patient encounter (evidence quality C).
- Developing policies that limit visitation through signage and education decreases spread of communicable diseases to the most vulnerable patient populations (evidence quality B).

References for this article are at http://pedsinreview.aappublications.org/content/39/3/107.

PIR Quiz

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3. To learn how to claim MOC points, go to: http://www.aappublications.org/content/moc-credit.

1. A 15-year-old girl with cystic fibrosis is admitted to the hospital for an acute pulmonary exacerbation. Her most recent sputum culture from the cystic fibrosis clinic grew multidrug-resistant *Pseudomonas aeruginosa*. Which of the following are the most appropriate transmission-based precautions for this patient?

   A. Airborne precautions.
   B. Contact precautions.
   C. Contact and droplet precautions.
   D. Droplet precautions.
   E. Standard precautions only.

2. A previously healthy 7-month-old girl is admitted to the hospital for bronchiolitis in January from the emergency department with a 3-day history of congestion, worsening cough, and decreased feeding. Her oxygen saturation level on room air is 86%. Respiratory syncytial virus and influenza virus are circulating at epidemic levels in the community. Which of the following is the most appropriate initial transmission-based precautions for this patient?

   A. Airborne precautions.
   B. Contact precautions.
   C. Contact and droplet precautions.
   D. Droplet precautions.
   E. Standard precautions only.

3. A previously healthy 18-month-old boy is seen in the office with a 7-day history of cough, decreased feeding, and intermittent fever. His grandmother emigrated from India 2 months ago and lives with the family. The grandmother was diagnosed yesterday as having active tuberculosis. A surgical mask is placed on the infant by the nurse when he arrives at the office and is put in an examination room immediately. The infant is subsequently admitted to the hospital for suspected tuberculosis and is placed in airborne precautions. How long should the examination room that the infant was seen in be left vacant before being used again?

   A. At least 1 hour.
   B. Fifteen minutes.
   C. Forty-eight hours.
   D. The room can be used immediately.
   E. Twenty-four hours.

4. A 4-month-old girl is admitted to the hospital with a 3-day history of fever, increasing irritability, and vomiting for the past day. A lumbar puncture shows cloudy cerebrospinal fluid (CSF). She is started on intravenous ceftriaxone and vancomycin and is placed in isolation with droplet precautions. The CSF polymerase chain reaction is positive for *Neisseria meningitidis*. Which of the following represents the best time to safely discontinue the droplet precautions for this patient?

   A. At the end of her 7-day course of antimicrobial therapy.
   B. Five days after admission.
   C. Immediately because only standard precautions are indicated for *N meningitidis* meningitis.
   D. Twenty-four hours after antibiotics were first administered.
   E. When a repeated CSF culture is negative for *N meningitidis*.

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5. A 9-year-old boy with acute lymphocytic leukemia was admitted to the hospital 4 days ago for neutropenic fever and developed diarrhea the past day. He has been receiving intravenous cefepime since admission. Stool *Clostridium difficile* assay is positive. Which of the following is the most appropriate method of hand hygiene for those caring for this patient?

   A. Alcohol-based foam.
   B. Alcohol-based lotion.
   C. Alcohol-based ointment.
   D. Chlorhexidine wipes.
   E. Soap and water.

Pediatric Intracranial Hypertension

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Education Gap

Intracranial hypertension can lead to significant morbidity; because it is a rare disorder, the general practitioner can easily miss cases.

Objectives

After completing this article, readers should be able to:

1. Recognize the clinical features of intracranial hypertension.
2. Understand the basics of the ophthalmologic examination.
3. Recognize potential causative factors contributing to intracranial hypertension.
4. Appropriately initiate the evaluation in suspected cases and start management in confirmed cases.

Abstract

Headaches are common in the clinical setting. Fortunately, intracranial hypertension (IH) is rare, but when present it can lead to significant morbidity. Early diagnosis and proper management are important to lessen the potential morbidity. Careful headache history, ophthalmologic examination, head imaging, and lumbar puncture (LP) are crucial tools in the diagnosis of this condition. Management should be coordinated with a neurologist, ophthalmologist, or neuro-ophthalmologist.

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ABBREVIATIONS

BID	twice daily
CSF	cerebrospinal fluid
ICP	intracranial pressure
IH	intracranial hypertension
LP	lumbar puncture
MRI	magnetic resonance imaging
ONSF	optic nerve sheath fenestration
PIH	primary intracranial hypertension
SIH	secondary intracranial hypertension

CASE PRESENTATION

Two patients present to your general pediatric clinic with separate complaints but related pathology. The first is a 16-year-old girl with a chief complaint of headache. She reports a daily headache for the past 3 weeks that is worse in the morning and improves over the course of the day but never resolves. On examination she is obese (BMI, 29) but is otherwise well-appearing. Funduscopic examination reveals blurred disc margins bilaterally. Visual field testing by direct confrontation notes constricted peripheral vision on the right side. The next patient is a well-appearing 6-year-old boy who presents after failing his vision screening at school. He denies any symptoms, but his mother interjects that he has been complaining of “seeing two of things” intermittently for the past few months. On examination he is a well-appearing boy with normal growth indices. He has a slight left esotropia and complains of diplopia when looking to the far left. Funduscopic examination reveals blurred disc margins bilaterally.

DEFINITION

The first description of IH in the literature was by Quincke in 1897, and he labeled it *meningitis serosa*. (1) Since this initial publication, advances in medicine have resulted in a multitude of names, including *serous meningitis, toxic hydrocephalus, otitic hydrocephalus, hypertensive meningeal hydrops, pseudotumor cerebri, benign intracranial hypertension, idiopathic intracranial hypertension,* and *pseudotumor cerebri syndrome*. Today, *pseudotumor cerebri* and *idiopathic intracranial hypertension* are the 2 terms most often used by physicians and the public. Unfortunately, the term *pseudotumor cerebri* can become confusing when a cause for the IH is found; thus, we prefer the terms *primary IH (PIH)* and *secondary IH (SIH)*. Primary refers to cases where no clear causative agent for the increased intracranial pressure (ICP) is found, replacing the terms *idiopathic intracranial hypertension* and *pseudotumor cerebri*. Individuals can have risk factors such as female sex, postpubertal status, obesity, or polycystic ovarian syndrome; however, these factors are not believed to directly result in increased pressure.

The term *SIH* is reserved for patients whose IH is the direct result of another condition (Table). Cerebral venous sinus thrombosis is a common cause of SIH, with the most frequent locations being the superior sagittal and transverse sinuses. Standridge and O’Brien (2) found that 11% of patients with IH had evidence of thrombosis on imaging without clear risk factors, highlighting the importance of obtaining a magnetic resonance venogram on all patients. It used to be common for patients with otitis or mastoiditis to present with IH due to sigmoid and/or jugular thromboses, previously referred to as otitic hydrocephalus. Fortunately, the modern use of antibiotics for these infections has greatly reduced the frequency of cases. Hypercoagulability in the acute postpartum period, oral contraceptive use, cancer, and various inherited coagulopathies can result in thrombosis and thus SIH. Because cerebrospinal fluid (CSF) is reabsorbed into the venous circulation, the prevailing theory is that the increased venous pressure results in reduced reabsorption and thus increased ICP.

Infection involving the intracranial components, such as meningitis or meningoencephalitis, can also result in SIH. Intracranial hypertension is an early presentation in bacterial meningitis, probably due to cerebral hyperemia. Later presentation of SIH is due to cerebral edema, obstructive hydrocephalus, infarction, and venous thrombosis resulting from the infection. The literature is filled with case reports of disseminated Lyme infection and IH. Presentation is often early in the course and is believed to be the result of decreased CSF absorption resulting from meningovascular inflammation.

Craniosynostosis due to premature closure of multiple sutures can lead to IH due to reduced intracranial volume and distortion of the intracranial venous sinuses.

The Table lists medications that have been strongly linked with SIH. Minocycline, tetracycline, and doxycycline have long been known to cause SIH. This is notable because many pediatricians use minocycline as first-line treatment of acne and are not aware of this potential adverse effect. Secondary IH due to minocycline has 3 separate presentation periods in relation to medication initiation: early (2 months), delayed (>2 months), and indeterminate (asymptomatic). Cessation of the medication results in return to normal pressure within 1 month, although rarely some patients continue to have symptoms.

Patients receiving growth hormone replacement for growth hormone deficiency can develop symptoms of IH. The most common scenario is complaints of headache and subsequent discovery of optic nerve edema. Patients typically present during the first 12 weeks of treatment, although it can occur at any time. Treatment consists of acetazolamide and cessation of the growth hormone until symptom resolution. Once all symptoms have resolved, patients can be started on a lower dose with gradual titration often without return of symptoms.

Long-term corticosteroid use can result in SIH; it is felt to be due to the weight gain associated with long-term corticosteroid use. A rapid wean or withdrawal is linked to a rebound increase in ICP and symptoms consistent with SIH. Gradual weaning with reduction by no more than 50% over the course of a few weeks reduces the chance of occurrence.

The adult criteria for PIH are referred to as the modified Dandy criteria. These criteria stipulate that a patient has 1) signs and symptoms of raised ICP (headache, nausea, vomiting, transient visual obscurations, or papilledema), 2) absence of localizing neurologic signs except for unilateral or bilateral abducens nerve palsy, 3) CSF opening pressure greater than 25 cm H_2O with normal composition, and 4) normal to small ventricles as demonstrated by computed tomography (today, magnetic resonance imaging [MRI] is the modality of choice). (3)

TABLE. Common Causes of Secondary Intracranial Hypertension

MEDICAL CONDITIONS	MEDICATIONS
Cerebral venous thrombosis	Tetracycline class (minocycline/tetracycline/doxycycline)
Meningitis/meningoencephalitis	Growth hormone
Intracranial hemorrhage	Corticosteroids (especially withdrawal)
Brain tumor	Lithium carbonate
Lyme disease	Cyclosporine A
Demyelinating disease/multiple sclerosis	Cytarabine
Leukemia/lymphoma	Nalidixic acid
Pregnancy/eclampsia	Retinoic acid
Crohn disease	Vitamin A excess
Hydrocephalus	Vitamin D (deficiency)
Craniofacial syndrome	Oral contraceptives (likely secondary to venous thrombosis)
Chiari malformation	
Traumatic brain injury	
Refeeding syndrome	
Adrenal insufficiency (often on corticosteroids)	
Hypoparathyroidism (early in correction)	
Vitamin A deficiency	

Further revisions to the criteria for PIH by Friedman and colleagues (4) have attempted to update the criteria and include requirements for pediatric cases and those presenting without optic nerve edema. Concerns have been raised that these stringent criteria will result in missed cases and increased potential morbidity. The pediatric normative values for CSF opening pressure have recently received scrutiny. Older studies determined normal opening pressures of 18 cm H_2O or less for children younger than 8 years and of 25 cm H_2O or less for children 8 years or older (mirrors adult normal values). Recent articles have questioned these values. Using 44 pediatric patients who had a sedated LP, Lee and Vedanarayanan (5) found a mean opening pressure of 20.3 cm H_2O. Avery et al (6) observed a mean opening pressure of 19.8 cm H_2O, and the 90th percentile for their cohort was 28 cm H_2O. They also found increases with moderate sedation and increased BMI. Both studies included patients with demyelinating and white matter disorders as well as healthy patients. Other published studies have shown increased opening pressures in patients with demyelinating conditions. Lee et al conducted a separate analysis of patients diagnosed as having demyelinating disorders and found that they had a mean opening pressure of 21.5 cm H_2O, higher than the total population mean of 20.3 cm H_2O. Morgan-Followell and Aylward (7) evaluated age- and sex-matched cohorts of patients with demyelinating conditions and PIH for comparison and found no statistically significant difference in the opening pressure between the 2 groups. This suggests that demyelinating conditions have elevated opening pressures and that including them in a normative population may falsely elevate the average. Fortunately, the debate surrounding the normal pressure is rarely needed because patients often have opening pressures well above either cutoff point. However, to avoid additional morbidities by missing cases, the authors prefer to use the older criteria.

EPIDEMIOLOGY

Traditionally, PIH is thought of as a rare disease. Outside the United States, the annual pediatric incidence is estimated to be 0.47 per 100,000 in Germany and 0.6 to 0.9 per 100,000 in the provinces of Nova Scotia and Prince

Edward Island. A recent study found an annual US PIH incidence of 0.63 per 100,000 children in a typical Midwestern city. (8)

Pediatric PIH is typically divided into prepubertal and pubertal groups. Those who have entered or completed puberty have the same risk factors as adults. Studies have shown a near 1:1 female to male distribution in prepubertal patients compared with the 4:1 ratio seen in adults. (9) In 2 separate studies, obesity was not shown to increase the risk of PIH in prepubertal patients. Examination of pediatric patients in a large IH registry found a significantly higher BMI (30.7 versus 21.6) in postpubertal patients with PIH compared with their prepubertal counterparts. (10)

The literature contains few reports of familial links with PIH, mostly parent and offspring relationships. Affected siblings have also been reported.

CLINICAL ASPECTS AND DIAGNOSIS

There is variability in clinical presentation depending on age (see the case presentations at the beginning of the article), with symptoms tending to be less evident in younger individuals. In prepubertal children, optic disc edema incidentally discovered on routine eye examination is reported in up to 33% of patients. Asymptomatic children are typically boys, younger, and less likely to be obese compared with their symptomatic counterparts.

The most common symptom reported is headache, in up to 96.5% of patients. The headaches are usually constant, with some variability in severity throughout the day. They are most often severe in the morning and can be exacerbated by maneuvers such as Valsalva, lying supine, bending over, or coughing.

The ophthalmic examination is crucial for the diagnosis and subsequent management of IH. The fundamental parts include pupillary and ocular motility assessments, color vision testing, visual acuity, and funduscopic examination (with attention to the optic nerve). Humphrey or Goldmann visual field testing, optical coherence tomography of the retinal nerve fiber layer, and fundus autofluorescence are useful tools for initial evaluation and serial monitoring.

Optic disc edema is frequently seen in IH and is often bilateral. Any patient presenting with unilateral edema should raise concerns for other diagnoses, such as optic neuritis. Up to 17.8% lack optic edema at presentation but have other symptoms consistent with elevated ICP (headache, nausea, vomiting, transient visual obscurations) and documented elevated opening pressure. The exact mechanism by which optic disc edema develops is poorly understood, and those lacking edema are believed to have unique anatomical variants at the level of the optic canal.

At presentation, up to 85% of patients able to participate in visual field testing demonstrate a visual field abnormality. Enlarged blind spots are the most common visual field defect, with peripheral constriction, nasal field loss, and inferior arcuate defects also seen. Visual acuity is often not affected unless severe edema is present and thus should not be used as a method to exclude the diagnosis of IH or to monitor progress. Transient visual obscurations are often reported as brief episodes (<30 seconds) of monocular or binocular blurring or "graying out" of vision. Events occur multiple times per day and can be provoked by position changes.

Cranial nerve VI palsy is seen in 12% to 60% of patients. Patients often note diplopia when looking in the direction of the nerve palsy. Often unreported until asked, pulsatile tinnitus is experienced by up to 44.3% of patients. Distinct from common tinnitus, it is often described as a "whooshing" sound coinciding with the heartbeat.

Direct funduscopic examination is used to visualize the optic nerve for the presence of edema and, if present, is graded using the Frisén scale. (11) The Figure contains clear examples of the different grades of optic edema. (9) Spontaneous venous pulsations are seen in 87% to 90% of the healthy population. They have also been seen in those with documented elevated ICP, making decisions regarding further evaluation and treatment difficult. The help of an ophthalmologist should be solicited for detailed evaluation of these findings.

If the child is able to cooperate, Humphrey or Goldmann visual field testing is performed at the initial and subsequent visits. These tests evaluate the peripheral vision using a dome-shaped screen on which visual targets are projected in static (Humphrey) or dynamic (Goldmann) fashion. The ability to maintain gaze fixation for 15 to 30 minutes is essential for visual field test reliability; thus, usually these tests are performed on older, more cooperative children. Optical coherence tomography is a noninvasive test that evaluates the thickness of the retinal nerve fiber layer surrounding the optic nerve and is used to monitor the resolution of papilledema during treatment.

It is important to note that optic disc drusen, globular aggregates of hyaline and calcium salts on the optic nerve, can mimic optic nerve edema. When this occurs, the patient is said to have pseudopapilledema. B-scan ultrasonography and fundus autofluorescence photography can be used by the ophthalmologist to differentiate between true papilledema and pseudopapilledema. Optical coherence tomography has been explored as a method of differentiating between the two as well, but as yet this method is

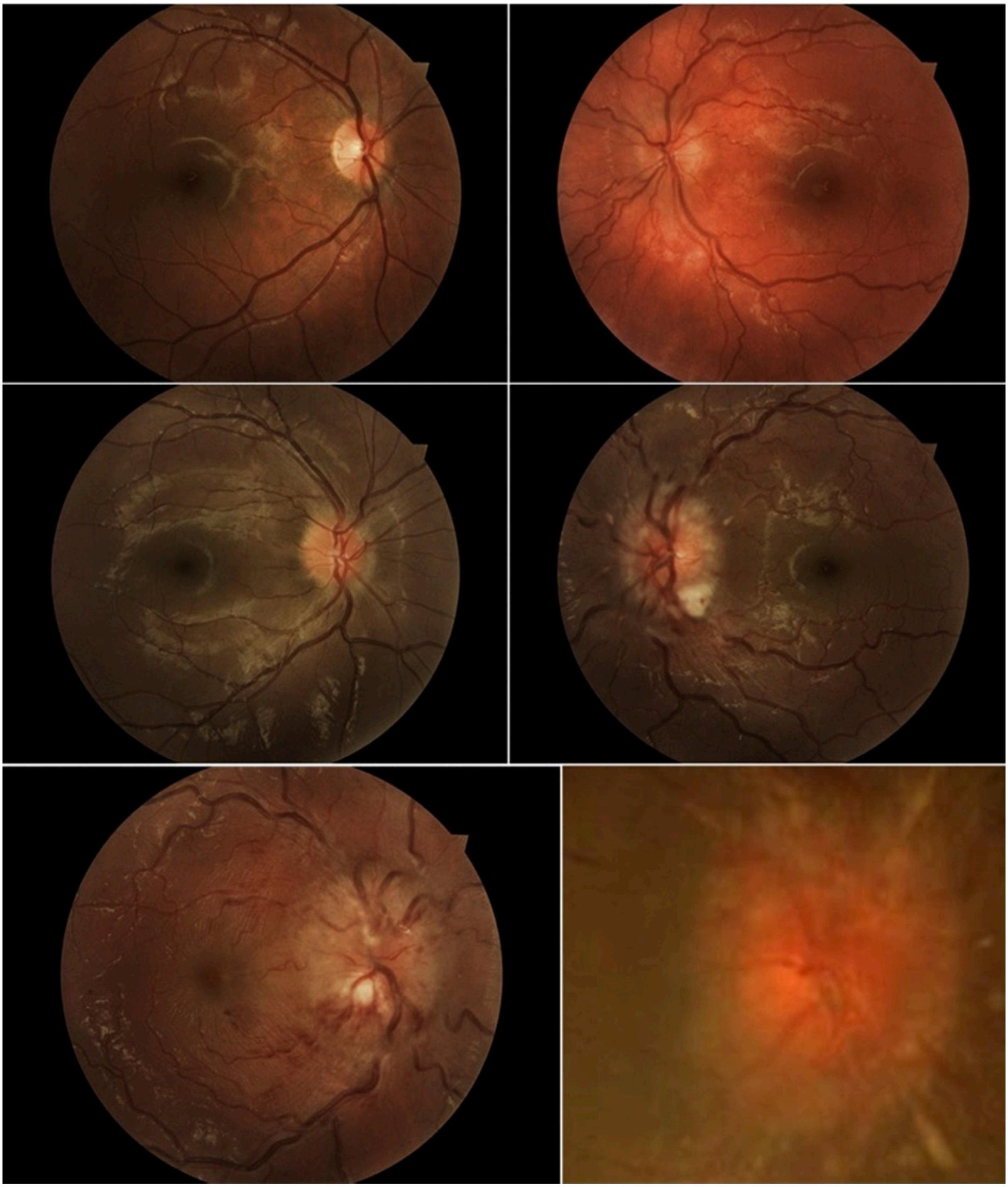

Figure. Optic nerve edema stages. Left to right. Top row: normal (0), stage 1. Middle row: stage 2, stage 3 (note cotton wool spot with hemorrhage at 5 o'clock). Bottom row: stage 4 (note hemorrhages at 1-2 and 6-8 o'clock, retinal striae due to severity of edema), stage 5. (Reprinted with permission from Elsevier. [9])

somewhat less reliable. The most reliable method is currently fluorescein angiography. (12)

Neuroimaging (computed tomography or MRI) should be performed as an initial step in the evaluation to rule out mass lesion, hydrocephalus, or other conditions that would be a contraindication to performing the LP. All pediatric patients diagnosed as having IH should eventually undergo MRI and magnetic resonance venography to rule out other secondary causes, such as sinus venous thrombosis. Although the MRI should be devoid of structural abnormalities, subtle findings suggestive of IH can sometimes occur, including empty or partially empty sella turcica, dilation of the optic nerve sheath, flattening of the posterior globe, anterior protrusion of the optic nerve head, tortuosity of the optic nerve, and distal transverse sinus stenosis. Although the presence of 1 or more of these subtle radiographic findings increases the probability of IH, lack of these findings does not decrease its likelihood. Bilateral transverse sinus stenosis is thought to be a consequence and not a cause of the IH as studies have shown normalization of the stenosis after high-volume LP. (13)

One of the most important diagnostic tools, and also the most fraught with error, is the LP. The most common error is improper positioning. Opening pressure measurements should not be performed with the patient in the seated position. Accepted positioning is in lateral decubitus with the legs and head extended at the time of pressure measurement. For sedated patients, spontaneous respirations with normal arterial carbon dioxide is preferred. One pediatric study found that an increase of 1 kPa in end-tidal carbon dioxide increases CSF pressure by 3.5 to 12 cm H_2O.

Popular convention is for withdrawal of large CSF volumes and normalization of the pressure in an effort to protect the vision. An adult study found that the average time to return to initial pressure after LP is 82 minutes. The authors' experience found that normalizing higher pressures results in increased rates of post-LP headache. Reduction of less than 10 cm H_2O of pressure still results in transient headache relief with fewer post-LP headaches.

MANAGEMENT

Management of a patient with IH often requires a multidisciplinary approach with neurology and ophthalmology. If clinically indicated, neurosurgery, psychology, psychiatry, dietetics, physical therapy, hematology, and/or endocrinology may be involved.

Often, pubertal and adult patients report weight gain in the 12 months before diagnosis. Numerous adult studies have shown that aside from removing an offending medication, weight loss is the only other modifiable risk factor shown to affect the ICP. One of the first studies treated patients with a low-calorie rice diet to treat their IH. (14) Study participants lost 11 to 56 kg over the treatment period, resulting in papilledema resolution without medication use. The 2 symptomatic patients reported complete resolution of symptoms in addition to resolution of their papilledema.

The goal of pharmacologic management is to decrease CSF production and in turn lower the ICP. Acetazolamide is considered the first-line treatment for IH due to its relative tolerability and lack of need for repeated laboratory monitoring. Patients may complain of food having a metallic taste to it, especially carbonated beverages. Transient paresthesia, metabolic acidosis, and slight increase in urination are other common adverse effects. The metabolic acidosis is often asymptomatic, and patients tolerate serum carbon dioxide levels down to 15 mmol/L without the need for supplementation. The typical adolescent dosing is 1 to 2 g divided twice daily (BID). Doses greater than 2 g failed to show much added benefit at the risk of increased adverse effects. In younger children, doses of approximately 20 to 25 mg/kg per day divided BID are typical, although doses as high as 100 mg/kg per day can be tolerated.

Furosemide is the second-line agent due to its diuretic nature and requirement to monitor for hypokalemia. Fortunately, most pediatric patients taking furosemide do not need potassium replacement above increased dietary intake. Typical dosing is 1 to 2 mg/kg per day divided BID. Studies have shown a synergistic effect when used in combination with acetazolamide.

Due to similar chemical structures to sulfonamides, there is a potential risk of cross-reactivity to acetazolamide and furosemide in patients with reported allergy. An adult study reviewed the medical records of patients with self-reported sulfa allergy who were given regimens of acetazolamide, furosemide, or a combination for treatment of IH. (15) No evidence of cross-reactivity was found, and the study suggests that patients with a reported sulfa allergy can safely take these medications.

Topiramate is also used in patients who are not able to tolerate acetazolamide or furosemide. It is similar to acetazolamide and has a similar mode of action. In an open-label study, 40 adult patients were alternately assigned to receive topiramate (100–150 mg/d) or acetazolamide (1,000–1,500 mg). Visual field grades were followed, and both treatment groups demonstrated statistically significant improvement.

Long-term use or rapid weaning of corticosteroids can result in SIH, although they used to be the first-line choice for treatment of PIH before acetazolamide. Their use has declined given the improved outcomes and fewer adverse effects with medications used today. However, in instances of severe visual deficits at presentation, corticosteroids used in conjunction with acetazolamide does result in a better outcome. The recommended dose is largely anecdotal, mirroring what is used in optic neuritis and other inflammatory neurologic disorders. Patients are initially given intravenous methylprednisolone 20 mg/kg (maximum 1 g) daily for 5 days followed by an oral taper.

In pediatrics, surgical interventions for IH are rarely necessary. Surgery is considered in patients for whom medical therapy cannot be tolerated, patients with severe optic nerve swelling with concerns of permanent vision loss, or patients with persistently elevated ICP with associated papilledema or pain despite maximizing pharmacologic options. The main procedures considered involve CSF shunting and optic nerve sheath fenestration (ONSF).

It is believed that ONSF preserves optic nerve function by redirecting pressure away from the optic nerve head, the area of the most tenuous blood supply. It does not directly address the elevated ICP. Surgery involves exposing the optic nerve and making openings in the sheath to relieve the pressure. Risks include ischemic optic neuropathy (especially in severely edematous or ischemic nerves), transient blindness, pupillary mydriasis and retrobulbar hemorrhage. Unilateral fenestration can result in resolution of edema in the unfenestrated eye; however, common practice is to perform bilateral fenestration. Typically, ONSF is not performed on an acutely swollen nerve but rather when the swelling is more under control. Signs of optic nerve ischemia, including cotton wool spots, increase the risk to the optic nerve and thus should resolve before the procedure is performed.

A CSF diversion is more effective in patients when pain is the primary symptom. In addition, it is used to protect vision in the acute presentation, where the risk of ischemic neuropathy due to ONSF is high. There are 2 options for shunt placement: lumboperitoneal or ventriculoperitoneal. The goal is to mechanically reduce the CSF pressure by direct CSF diversion. Unfortunately, the myth that ventricular diversion is superior still persists. In one study, the outcomes of 25 patients shunted for their IH were reviewed. (16) Shunt failure was defined as continuation or return of presenting symptoms with radiographically verified shunt placement and normal opening pressure. Those requiring revision had radiographic evidence of shunt disturbance, blockage, or increased opening pressure. Failure rates were similar at 11% and 14% for lumbar and ventricular shunts, respectively. Revisions were more common in lumbar versus ventricular shunts (60% versus 30%).

Attempts have been made to stent sinus venous stenosis in adults with varying success. Headache resolution is seen in up to 84.6% of patients, and resolution of papilledema in 62.5% to 100%. Transient postoperative headache or partial hearing loss on the treated side are the most common adverse effects reported. Rarer adverse effects include hemorrhage, venous perforation due to the guidewire, and temporary unsteadiness. Use of stenting has not been studied in pediatrics.

PROGNOSIS

Despite the previously held belief that this is a relatively benign condition, the potential for permanent vision loss and chronic pain are significant morbidities. When properly treated, headaches typically resolve within the first few weeks. Resolution of papilledema averages 4.2 to 5 months. Minor visual field deficits often fully resolve, sometimes lagging behind resolution of the papilledema. There is literature to suggest that grade 3 or higher papilledema is a high predictor of permanent visual deficits. Another study found that postpubertal status resulted in a worse visual outcome. Recurrence is seen in 18% to 20% of patients. A series of adult patients were followed after weaning off acetazolamide for recurrence of their optic nerve edema. (17) All the patients lost weight from the time of diagnosis to medication wean, and those with recurrence had an average BMI 5.5% higher than at diagnosis. This was compared with an average decrease of 17.9% in BMI in those without recurrence.

Up to two-thirds of patients develop new headache symptoms that are reported as different from their IH headache. Most are diagnosed as having migraine without aura or episodic tension-type headache and respond to common prophylactics used for these conditions.

Summary

- Based on research evidence, obesity does not play as large of a role in primary intracranial hypertension in prepubertal patients. (6)(7)
- Consensus supports the crucial role of the ophthalmic examination in diagnosis and subsequent management of intracranial hypertension. This includes pupillary and ocular motility assessments, color vision testing, visual acuity, funduscopic examination, Humphrey or Goldmann visual field testing, and optical coherence tomography.
- Based on strong research and consensus, the lumber puncture opening pressure measurement should be performed with the patient in the lateral decubitus position with the legs and head

extended. Sedated patients should have spontaneous respirations with normal arterial carbon dioxide concentrations.

- The literature supports the consensus that minocycline, and the related tetracycline class of medications, can cause secondary intracranial hypertension. This is of concern because many pediatricians use minocycline in the treatment of acne and are not aware of this potential adverse effect.
- Based on strong research studies, aside from removing an offending medication, weight loss is the only modifiable risk factor shown to affect the intracranial pressure and prevent recurrence. (11)(14)
- Based on research and consensus, acetazolamide is the first-line treatment for intracranial hypertension due to its relative tolerability and lack of need for repeated laboratory monitoring.
- Some research has shown that lumbar shunts have equal failure rates compared with ventricular shunts. (13)

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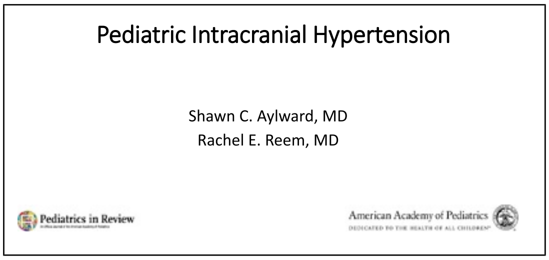

Pediatric Intracranial Hypertension

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Pediatrics in Review

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1. A 14-year-old girl presents to the clinic for a health supervision visit. She has a history of primary intracranial hypertension, which is now resolved. She is concerned about facial pustular acne, especially as she starts high school. Which of the following medications would be the most appropriate first-line treatment for this patient?
   A. Clindamycin/tretinoin.
   B. Erythromycin/benzoyl peroxide.
   C. Minocycline.
   D. Oral contraceptives.
   E. Retinoic acid.
2. A 9-year-old obese boy is seen in an urgent care clinic for headaches and vision problems for the past 2 weeks. According to the modified Dandy criteria, the presence of which of the following would exclude a diagnosis of primary intracranial hypertension?
   A. Abducens palsy.
   B. Enlarged blind spot.
   C. Localizing neurologic signs.
   D. Spontaneous venous pulsations on funduscopic examination.
   E. Transient visual obscurations.
3. You refer a 5-year-old boy to the ophthalmology clinic because his mother is concerned that he dislikes reading and holds his book too far away from his face. You receive a call from the ophthalmologist stating that his visual acuity is normal but he has bilateral optic disc edema. Which of the following best represents the percentage of prepubertal pediatric patients that have optic disc edema incidentally discovered on routine eye examination?
   A. 1%.
   B. 10%.
   C. 20%.
   D. 25%.
   E. 30%.
4. After receiving a lumbar puncture and confirming that his cerebrospinal fluid pressure is elevated at 30 cm H_20, the patient described in Question 3 is started on acetazolamide. His mother would like to know how long the papilledema will take to resolve.
   Which of the following represents the average time that it takes for papilledema to resolve?
   A. 2 weeks.
   B. 6 weeks.
   C. 2 months.
   D. 5 months.
   E. 1 year.
5. A 13-year-old girl who presented with headaches at age 12 years and was diagnosed as having primary intracranial hypertension returns to the clinic with recurrence of her headaches after weaning her off acetazolamide. She also notes nausea and photophobia. You suspect a diagnosis of migraines but wonder whether you should check a cerebrospinal fluid opening pressure. Which of the following represents the recurrence rate of primary intracranial hypertension?
   A. 10%.
   B. 20%.
   C. 30%.
   D. 40%.
   E. 50%.

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Acute Abdominal Pain

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Education and Practice Gaps

Children frequently have acute abdominal pain. The physician must identify which child has a potentially catastrophic condition (<2%). Because the number of patients requiring immediate action is low, the physician can be lulled into a sense of safety. Infrequently, acute abdominal pain can be catastrophic, so the physician needs to be cognizant of conditions requiring action. Knowledge and judgment are key.

Objectives After completing this article, readers should be able to:

1. Understand the causes and frequency of acute abdominal pain in childhood.
2. Develop a differential diagnosis based on age and symptoms.
3. Formulate a plan for evaluation and management of acute abdominal pain.
4. Choose the appropriate imaging study for various diagnoses.

Acute abdominal pain is a frequent and challenging problem facing pediatricians. The cause of acute abdominal pain can range from John Apley's "little bellyacher" (1) to an emergency requiring immediate action. Assessing acute abdominal pain is a situation that requires excellent clinical acumen, an area where pediatricians should "prove their worth" by outperforming other primary caregivers. Making the correct diagnosis may earn the pediatrician accolades for saving a life (as in the case of intussusception or midgut volvulus) but may also not win friends (as when a mother is informed that the reason for her child's excruciating pain is constipation). A mistaken diagnosis can have devastating results, either by not acting when action is called for or by performing unnecessary tests and procedures.

Because the differential diagnosis list for acute abdominal pain is long, a logical approach is to consider diagnoses by age group. Convenient age divisions are neonates, 0 to 2 months; infants, 3 to 12 months; preschoolers, 1 to 5 years; children, 6 to 11 years; and adolescents, 12 to 18 years. Within each of these groups a diagnosis can be categorized as common or uncommon and as serious or less serious (Tables 1 through 5). (Note that designation as "serious" and "less serious"

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ABBREVIATIONS

CRP	C-reactive protein
CT	computed tomography
DRE	digital rectal examination
ERCP	endoscopic retrograde cholangiopancreatography
GI	gastrointestinal
HIDA	hydroxyiminodiacetic acid
IV	intravenous
MRI	magnetic resonance imaging
TPN	total parenteral nutrition
WBC	white blood cell

TABLE 1. **Causes of Acute Abdominal Pain in Neonates (Aged 0–2 Months)**

	SERIOUS	LESS SERIOUS
Common	Necrotizing enterocolitis Adhesions	Colic
Uncommon	Volvulus Testicular torsion	Dietary protein allergy

is subjective but is based on whether immediate action is required. Diagnoses are not listed in order of frequency.)

Abdominal pain is perceived via mucosal or serosal receptors. These pain receptors are located on serosal surfaces, in the mesentery, and in the intestinal wall. Abdominal pain is poorly localized, often being perceived as midline, until the serosal surface becomes affected, as in appendicitis; then better localization occurs. (2) Children younger than 5 years are not able to localize pain well. A young child with acute otitis media may complain of abdominal pain.

For most children with acute abdominal pain, the pain is short, self-resolving, and non–life-threatening. In a study that included almost 1,000 children aged 4 to 18 years, close to 10% had at least 1 episode of acute abdominal pain that came to medical attention. Constipation accounted for 48% of these episodes, and 19% of the episodes went undiagnosed. Only 2% had a surgical cause for acute abdominal pain. (3) For the few that have conditions that require immediate action, age at onset, concomitant signs, symptoms, or history frequently lead to the correct disposition. For this reason, a detailed history, including history of the present condition, past medical history, and family history, and a complete physical examination (not just the abdomen) are essential. The digital rectal examination (DRE) has the potential to add important information regarding the cause of acute abdominal pain. A DRE can quickly establish the presence of constipation. Although constipation is a frequent cause of pain, the child with constipation may have acute abdominal pain due to unrelated causes. Frequently, laboratory investigation and imaging are performed. The results of these tests, along with age, history, and physical examination findings, weigh into the final conclusion. Coming to the correct disposition of a patient with acute abdominal pain relies on assembling available information and then judiciously considering the likely diagnoses.

APPENDICITIS

Appendicitis is the most common abdominal surgical emergency in childhood, although it is relatively uncommon in children younger than 5 years (Tables 3 through 5). It can be rapidly progressive; from onset to perforation can be as short as 12 hours. Several scoring systems have been devised for the diagnosis of appendicitis in children. The 2 most widely used are the Alvarado score and the Pediatric Appendicitis Score. Both are based on similar parameters; however, the usefulness of both these scores has been questioned. (4) The scoring systems have been largely superseded by imaging studies that have changed the way in which appendicitis is diagnosed. The first is point of service ultrasonography. Ultrasonography has the obvious advantages of being readily available, being noninvasive, and avoiding radiation exposure. In the event that ultrasonography demonstrates appendicitis, it is highly specific. In a pediatric study, point of service ultrasonography confirmed a diagnosis in 51% of patients, thus avoiding computed tomography (CT). However, the usefulness of ultrasonography is limited, especially in obese children and in uncooperative children. Computed tomography remains the most accurate imaging study for diagnosing appendicitis. In many institutions it has become the imaging modality of choice. In one study it reduced the false-negative appendectomy rate from 23% to 1.7% in an 18-year period. At the conclusion of the study, essentially all of the patients who had surgery for appendicitis had a CT scan before surgery. (5) Because the radiation dose from a CT scan is high, efforts have concentrated on reducing the amount of radiation. A CT scan that uses lower levels of ionizing radiation and targeted CT scans have reduced radiation exposure. An avenue to eliminate radiation is the use of magnetic resonance imaging (MRI). As technology advances, MRI may become the imaging modality of choice; however, the time required for the study and the motion artifact are too great at present for routine use in diagnosing appendicitis. Serum markers, although nonspecific, can be of help. White blood cell (WBC) count with a lift shift and C-reactive protein (CRP) level in combination have 94% specificity. Definitive management remains surgery.

INTUSSUSCEPTION

Intussusception refers to invagination of a proximal segment of bowel (the intussusceptum) into a distal segment (the intussuscepens). The intussusceptum drags its mesentery with it into the distal bowel, leading to venous and lymphatic obstruction, ischemia, and perforation. This mechanism results in the classic triad of intermittent, severe abdominal pain, a sausage-shaped mass, and "currant jelly" stools. Especially early in the condition, intussusception can present with listlessness and a septiclike picture.

Intussusception can occur at any age, but it is the most common abdominal emergency in children 6 to 36 months of age (Tables 2 and 3). Within this age range, usually the terminal segment of the ileum invaginates into the cecum, creating an ileocolic intussusception. Peyer patches may act as the lead point of the intussusceptum. Hypertrophy of Peyer patches, as with viral illness or rotavirus vaccination, has been associated with intussusception. Other lead points are possible, especially outside the 6- to 36-month age range, including Meckel diverticulum, polyps, lymphoma, and duplications. Even after successful reduction of the intussusception, it is not unusual to have 1 or more recurrent episodes.

Because of improved diagnosis and treatment, the classic triad is now seldom seen. The more favorable outcome is most likely due to early diagnosis and more successful treatment. Ultrasonography has become the diagnostic method of choice, where the intussusception shows as a "target-shaped" finding. The specificity of ultrasonography approaches 100%. (6) Both CT and MRI are also excellent at visualizing an intussusception. Except in complicated or equivocal cases, there is seldom need to resort to these more complicated diagnostic imaging studies. However, the increased use of these studies in other situations has revealed that transient, self-resolving, asymptomatic small-bowel intussusceptions occur frequently and do not require treatment.

There are a variety of nonsurgical techniques for reducing an intussusception. These involve enemas (contrast, saline, or air) and some method of visualization (fluoroscopy or ultrasonography). Choice of technique is often institution dependent. However, the combination of warmed saline enemas and ultrasonography offers the advantage of excellent visualization along with avoidance of ionizing radiation. Chances of successfully reducing an intussusception depend on many factors, including the length of time that the symptoms have been present, the age of the patient, whether there is a lead point, and the location of the intussusception. If a reduction attempt is only partially successful and the patient remains stable, at least 3 nonsurgical reductions can be tried before resorting to surgery. The unstable patient should go directly to surgery. Nonsurgical reduction is successful approximately 80% of the time. Perforation occurs in less than 1% of patients during nonsurgical reductions. (7)

TABLE 2. **Causes of Acute Abdominal Pain in Infants (Aged 3–12 Months)**

	SERIOUS	LESS SERIOUS
Common	Foreign body ingestion Trauma	Constipation Gastroenteritis Viral illness Dietary protein allergy Urinary tract infection
Uncommon	Adhesions Hemolytic uremic syndrome Hirschsprung disease Intussusception Incarcerated hernia Sickle cell crisis Tumor	Hepatitis

CHOLECYSTITIS, CHOLELITHIASIS, CHOLEDOCHOLITHIASIS

Gallbladder disease in children is being diagnosed and treated with increased frequency. This increase is partly due to greater awareness and partly to the epidemic of childhood obesity (Tables 4 and 5). Cholelithiasis and gallbladder sludge was documented in 2.36% of children undergoing abdominal ultrasonography for any reason. (8) Factors that are known to predispose to gallbladder disease include total parenteral nutrition (TPN), hemolytic diseases, systemic infections, some antibiotics, biliary anatomical anomalies, cystic fibrosis, increased estrogen (pregnancy or oral contraception), a positive family history, and obesity. Interruption of the enterohepatic circulation can lead to gallstone formation, as in Crohn disease with ileal involvement and short small bowel with ileal resection. There is a racial (Amerindian) and a genetic predisposition to the development of gallstones. The composition of gallstones in children is different from that in adults. Classically, gallstones have been categorized as cholesterol stones

TABLE 3. **Causes of Acute Abdominal Pain in Preschoolers (Aged 1–5 Years)**

	SERIOUS	LESS SERIOUS
Common	Appendicitis Foreign body ingestion Intussusception Trauma	Constipation Viral illness Gastroenteritis Pharyngitis Urinary tract infection Pneumonia
Uncommon	Adhesions Hemolytic uremic syndrome Intra-abdominal abscess Diabetic ketoacidosis Ovarian torsion Sickle cell crisis Tumor	Henoch-Schönlein purpura Hepatitis

TABLE 4. Causes of Acute Abdominal Pain in Children (Aged 6–11 Years)

	SERIOUS	LESS SERIOUS
Common	Adhesions Appendicitis Diabetic ketoacidosis Inflammatory bowel disease Trauma	Constipation Viral illness Gastroenteritis Pharyngitis Urinary tract infection Pneumonia
Uncommon	Hemolytic uremic syndrome Perforated ulcer Primary bacterial peritonitis Hemolytic uremic syndrome Intra-abdominal abscess Myocarditis/pericarditis Pancreatitis Ovarian/testicular torsion Sickle cell crisis Tumor	Abdominal migraine Cholecystitis Henoch-Schönlein purpura Hepatitis Familial Mediterranean fever

and pigmented stones. Pigmented stones are subdivided into black stones and brown stones. Gallstones are seldom, if ever, pure. Cholesterol stones (which predominate in adults) are composed of only 50% cholesterol. The remainder is made up of glycoprotein and calcium salts.

TABLE 5. Causes of Acute Abdominal Pain in Adolescents (Aged 12–18 Years)

	SERIOUS	LESS SERIOUS
Common	Adhesions Appendicitis Diabetic ketoacidosis Inflammatory bowel disease Hemolytic uremic syndrome Pelvic inflammatory disease Trauma	Constipation Viral illness Gastroenteritis Pharyngitis Urinary tract infection Dysmenorrhea Pneumonia Ruptured ovarian cyst
Uncommon	Hemolytic uremic syndrome Perforated ulcer Primary bacterial peritonitis Intra-abdominal abscess Myocarditis/pericarditis Pancreatitis Sickle cell crisis Ovarian/testicular torsion Ectopic pregnancy Tumor	Abdominal migraine Cholecystitis Henoch-Schönlein purpura Hepatitis Familial Mediterranean fever Urolithiasis

Cholesterol stones are associated with obesity and cystic fibrosis and are less frequent in children than in adults. Black pigment stones are more common in children than in adults and are associated with hemolytic disease and TPN. Calcium carbonate stones (associated with systemic disease) and brown pigment stones (associated with bacterial infection) can occur in children. The presentation of cholelithiasis and cholecystitis in children is variable and less specific than the presentation in adults. Although in adults the combination of right upper quadrant pain with vomiting exacerbated by eating fatty food is suggestive of cholelithiasis, children may present with merely nonspecific, poorly localized pain. The classic presentation of cholecystitis in adults of right upper quadrant pain, vomiting, fever, and leukocytosis may not be present in children or may be obscured by other findings. Although biliary pain is described as colicky, this is a misnomer as the pain is usually perceived as "constant" by both adults and children.

The evaluation of a child suspected of having gallbladder disease should include a WBC count, inflammatory markers (erythrocyte sedimentation rate and CRP), liver function tests, amylase, and lipase. Imaging should be performed in any child with a suggestive history and/or physical examination findings, even if the laboratory test results are normal. Abdominal ultrasonography has a better than 90% accuracy for diagnosing cholelithiasis, (9) where stones show up as movable masses (in contradistinction to gallbladder polyps) of variable size. On ultrasonography, gallstones cast "shadows" that are pathognomonic. Gallbladder sludge is a frequent incidental finding on abdominal ultrasonography (1.46% of abdominal ultrasonography in children [8]). The significance of sludge is not clear. Some believe that sludge is a precursor to stones, and others believe that it has no long-term significance. Gallbladder wall thickening indicative of cholecystitis is less specific and can occur in hepatitis and with generalized edema. Gallbladder wall thickening should be interpreted in the context of other findings. Abdominal ultrasonography can assess intrahepatic and extrahepatic ducts, pancreas, and adjacent structures. HIDA scans are as accurate as ultrasonography in diagnosing cholecystitis. HIDA stands for hydroxyiminodiacetic acid, a radiopharmaceutical tracer that is no longer used for the scan, but the name has remained. A HIDA scan is performed by administering the radiotracer intravenously. The tracer is taken up by the liver and excreted via the biliary ducts. It shows up in the gallbladder within 1 to 4 hours. From a practical point of view, HIDA scans are not used for the diagnosis of cholecystitis because they require advanced planning and are not readily available. The HIDA scan does measure gallbladder excretion. Biliary dyskinesis (delayed gallbladder excretion demonstrated by HIDA scan) may be an uncommon cause of abdominal pain in children. Many children who undergo cholecystectomy for a decreased ejection fraction have postoperative recurrence of symptoms, bringing into question whether the gallbladder dysfunction was the true cause of the pain. (10) Endoscopic retrograde cholangiopancreatography (ERCP) is diagnostically useful in older children and teenagers. It has the distinct advantage that it can be therapeutic for common duct stones. (It can remove stones in bile ducts, stretch bile duct strictures, and place stents across a strictured area.) It is seldom performed in young children because the endoscopes are too large and pediatric endoscopists lack the skill to perform this procedure. Postprocedure pancreatitis is not uncommon. Magnetic resonance cholangiopancreatography has become increasing useful in complicated biliary disease as the quality and resolution of the technique has improved. It is as sensitive, perhaps more sensitive, than ultrasonography for the diagnosis of cholecystitis. It avoids radiation but usually requires sedation. It is not universally available.

Management of gallbladder disease varies with the age of the patient and the type of disease. In neonates with stones and no cystitis, symptomatic management and observation is usually adequate. Resolution without intervention can be expected. Resolution of stones associated with TPN may occur spontaneously. In older children the stones are unlikely to resolve without treatment. Autopsy data show that many people live and die with gallstones that never became symptomatic. For those found to have asymptomatic gallstones, elective removal is safe and simple, so cholecystectomy is a reasonable option in those who are at high risk for developing symptoms. Cholecystectomy for gallstones in hemolytic diseases, such as sickle cell disease and spherocytosis, is mandatory. Definitive surgery can usually be performed as an elective procedure.

Acute cholecystitis presents a more critical and more dangerous scenario. Presentation is characterized by severe right upper quadrant pain, sometimes radiating to the back. Vomiting is often present. Fever and jaundice occur in approximately one-third of affected children. Inflammation of the gallbladder adjacent to the serosa gives rise to a Murphy sign, which is severe, sharp pain with cessation of breathing on palpation of the right upper quadrant. Children with acute cholecystitis should be hospitalized, made nil per os, and administered intravenous fluids and pain medications. Consideration of intravenous antibiotics should be given, especially in the face of persistent fever. Laparoscopic removal of the gallbladder should occur when the child is stabilized.

PANCREATITIS

The apparent incidence of acute pancreatitis in children is rising; however, it is not clear whether this is a true increase or more awareness. In the United States, a rate of 13.2 cases per 100,000 children per year is reported, whereas only 3.6 cases per 100,000 children per year are reported in Australia (Table 5). (11)(12) Pancreatitis in adults and children probably share the same final pathway, but the initiating events differ. Gallstones and alcohol are the common underlying factors in pancreatitis in adults. In children, for one-third of cases no etiology is found. Systemic illness, biliary diseases, medications, trauma, and suspected infection account for most underlying etiologies. In addition, only 10% of childhood pancreatitis will progress to recurrent or chronic pancreatitis.

Any of the underlying etiologies mentioned (and perhaps others) can lead to pathologic activation of calcium signaling in the acinar cells of the pancreas that triggers intracellular activation of proteases. Predominantly, trypsinogen is converted to the active trypsin. This cascade leads to cytokine release, inflammation, edema, and cell destruction. Mechanisms to counteract pancreatic damage are pancreatic enzyme compartmentalization, trypsin autodegradation, and trypsin inhibition, including activation of serine protease inhibitor Kazal type 1 (SPINK1).

The diagnosis of acute pancreatitis is based on presentation, biochemical profile, and imaging. The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) listed guidelines for diagnosis, which include clinical findings of abdominal or back pain, nausea and vomiting, amylase or lipase levels greater than 3 times the upper limit of normal, and imaging findings consistent with pancreatitis. (13) Care must be exercised when eliciting and interpreting clinical findings. Epigastric pain is the most common finding, but diffuse abdominal pain is not uncommon in children. Infants and toddlers frequently do not have abdominal pain but frequently have fever and abdominal distention. Back pain, despite the fact that it is one of the classic symptoms, is rare. Likewise, ecchymosis of the flank (Grey sign) is almost never present. Nonverbal patients may not be able to indicate abdominal pain and may well be taking medications known to be associated with pancreatitis, such as valproic acid.

The imaging study of choice is controversial. Ultrasonography is almost always the first imaging study performed because it is readily available, avoids radiation, and gives information about the pancreas and about surrounding structures and other causes of pain. It is the best test to identify stones. However, obesity and bowel gas can limit assessment of the pancreas itself. The CT scan gives different information. It is the best test for assessing the complications of pancreatitis, such as hemorrhage, necrosis, and pseudocyst formation. (14) For this reason, it is frequently performed several days into treatment, when complications are suspected. There is not sufficient information on MRI for acute pancreatitis; however, with improving technology, it may become an option.

Other imaging studies used to further delineate causes of pancreatitis, such as magnetic resonance cholangiopancreatography, endoscopic ultrasonography, and ERCP, do not play a role in the diagnosis and treatment of acute pancreatitis except that ERCP is curative for pancreatitis due to a stone obstructing the common duct. In trauma-induced pancreatitis, ERCP can demonstrate the extent of ductal damage.

The treatment of acute pancreatitis consists of 3 elements: 1) pain management, 2) fluid management, and 3) nutrition. Morphine is the most widely used pain medication for acute pancreatitis in children, despite the concern that morphine might induce sphincter of Oddi spasm, thus worsening the pancreatitis. Narcotic-sparing medication and nerve blocks have been tried in adults, but there is no experience in children. Fluid therapy should be early and aggressive. During the first 24 hours, 2 to 3 times maintenance fluids should be administered. In the past, patients with acute pancreatitis were allowed nothing by mouth and often had a nasogastric tube placed and stomach contents suctioned. Patients often received intravenous nutrition. More recent studies have demonstrated that there is no need to avoid using the gastrointestinal (GI) tract for nutrition. Children with mild pancreatitis can be allowed a low-fat diet from the beginning of therapy. In more severe cases, nasogastric or nasojejunal feeding can be instituted within the first few days.

Antibiotics are not recommended as a routine therapy, even in severe pancreatitis; however, if superinfection is suspected, cultures should be obtained and broad spectrum antibiotics used until culture results can allow narrowing the antibiotic coverage.

For adults with acute pancreatitis, there are several scoring systems to predict the severity of the disease, including the Ranson criteria, the modified Glasgow scale, and the Apache II index. None of these are applicable to pediatric disease. In fact, there is no clear definition of what constitutes severe acute pancreatitis in a child. (15)

MALROTATION AND VOLVULUS

Midgut volvulus is a true surgical emergency. The time from the first signs of obstruction to necrotic bowel requiring resection can be a few hours. If resection of necrotic bowel becomes necessary, the bowel removed can include the small bowel from the duodenojejunal junction to the mid-transverse colon, including the ileocecal valve and cecum (the distribution of the superior mesenteric artery). A child who undergoes surgery of this extent will have extreme short bowel syndrome and interruption of the enterohepatic circulation. With only a few centimeters of small bowel remaining, the child will almost certainly be dependent on parenteral nutrition, and there is a high probability that a small-bowel transplant will become necessary. Small-bowel volvulus commonly (45%) occurs in the context of intestinal malrotation. Malrotation is the failure of the normal rotation and fixation of the bowel during organogenesis. The result is a cecum that is free to fold and unfold on itself, usually in the right upper quadrant. This folding and unfolding can lead to intermittent symptoms of obstruction and pain. Ladd bands extend from the cecum to the abdominal wall, crossing the duodenum. There can be duodenal obstruction from these bands. In malrotation, the small bowel is located on the right side of the abdomen, resulting in a narrow mesenteric root. This allows the intestine to twist around the mesentery, compromising the superior mesenteric artery with subsequent ischemia and bowel death. Volvulus of the small bowel can be due to adhesions or bands (30%), Meckel's diverticulum, or idiopathic. (16) Rotational abnormalities are thought to be present in 1 of 100 to 1 of 3,000 live births. However, the true incidence is not known because many are asymptomatic. Of the intestinal rotation abnormalities that come to medical attention, half will be found before a month of age and 90% will be diagnosed before a year (Table 1). However, midgut volvulus can occur at any age, so most surgeons will perform the Ladd procedure to alleviate intestinal malrotation when an incidental malrotation is discovered.

The diagnosis of small-bowel volvulus depends on a high index of suspicion. The most consistent finding is bilious and nonbilious vomiting. Abdominal distention may or may not be present. Abdominal pain is an inconsistent symptom. Laboratory abnormalities are not specific to volvulus but include leukocytosis, elevated CRP levels, and hyponatremia. The imaging study of choice is the contrast upper GI series, which is 96% sensitive and demonstrates abnormal positioning of the third and fourth portion of the duodenum in malrotation and the "corkscrew" sign when midgut volvulus is present. Ultrasonography has not replaced the upper GI series, although the midgut volvulus findings on ultrasonography include the "whirlpool" sign and inversion of the superior mesenteric artery and vein, with the superior mesenteric vein on the left anterior side of the superior mesenteric artery instead of its usual right side location. These ultrasonography findings are not as consistent as the upper GI series findings. (17)

Management of midgut volvulus is to proceed to corrective surgery as quickly as feasible. Initial therapy includes fluid resuscitation, evacuation of the stomach via nasogastric suctions, and broad spectrum antibiotics followed by definitive surgery. In one series, the resection rate was

44.9%, and 14.3% had postoperative complications, including short bowel syndrome, adhesions, intra-abdominal abscess, and failure to thrive. (16)

CONSTIPATION

Constipation is the most frequently identified cause of acute abdominal pain. It is not a medical emergency, but it often presents as such. Importantly, constipation causing a picture of acute abdominal pain almost certainly has been present for months, if not years. A careful history will reveal that such a child with constipation has a long history of difficulty defecating, with infrequent bowel movements. Bowel movements may be large and hard or small and pebbly. The bowel movements may be painful, and withholding behavior may be present. A history of daily soft-to-loose bowel movements does not exclude the possibility of constipation because constipation with overflow may be present. Physical examination may reveal multiple fecal masses felt through the abdominal wall; sometimes a single, large mass is palpable in the suprapubic area. A DRE may reveal hard stool in the rectal vault, or the vault may be empty, as in the case of Hirschsprung disease. Constipation has many etiologies (Table 6), but by far the most common is functional constipation, which is present in 0.7% to 29.6% of children. (18) Functional constipation is defined by the Rome III criteria; (19) however, just as useful is the working definition "infrequent passage of hard, uncomfortable stools that are distressing to the child." (20)

Acute abdominal pain caused by constipation is due to retention of fecal material anywhere in the colon. The pain is poorly localized, usually nonradiating. Mild tenderness to palpation is commonly present. History and physical examination should suggest constipation, but laboratory investigation and imaging are frequently necessary to exclude other diagnoses. In the constipated child, WBC count, CRP level, and electrolyte levels will be normal. Ultrasonography will not demonstrate appendicitis. The usefulness of an abdominal radiograph to diagnose constipation is questionable, (21) but it may be useful as a baseline in determining the results of treatment.

In the absence of obstruction (constipation rarely, if ever, causes complete obstruction), the current recommendation for acute abdominal pain due to constipation is to administer large-volume osmotic laxatives (lactulose or polyethylene glycol 3350) enterally, by mouth, or by nasogastric tube. Enemas are not recommended because they will not cleanse the entire colon and are not well tolerated. An abdominal radiograph can ensure that the colon is substantially free of fecal material. If not, a repeated colon cleanse is required. After evacuation of the colon, a maintenance regimen of daily stool softeners, daily toilet sitting, and improved diet is initiated.

TABLE 6. **Reasons for Defecation Difficulty**

Functional constipation	Infant dyschezia
Hypothyroidism, hypercalcemia, hypokalemia	Imperforate anus, anal stenosis
Celiac disease	Dietary protein allergy
Diabetes mellitus	Hirschsprung disease
Spinal cord anomalies, tethered cord	Cystic fibrosis
Opioids, anticholinergics, antidepressants	Abnormal abdominal wall, prune belly
Heavy metal ingestion (lead)	Gastroschisis, trisomy 21
Sexual abuse	Botulism
Vitamin D intoxication	

CONCLUSION

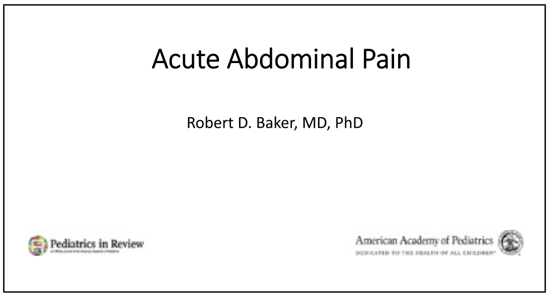
Acute abdominal pain in childhood is a frequent and challenging clinical symptom. The diagnoses are many and vary in severity, evaluation, and outcome. The clinician must exercise acumen to arrive at the correct diagnosis and must remain vigilant to identify the child who requires immediate treatment.

Summary

- Acute abdominal pain is a common occurrence. One in a hundred children will experience at least 1 episode of acute abdominal pain that will come to medical attention. However, most episodes are not emergencies. It is the rare episode that requires immediate and accurate action. (3) (Strength of evidence C. Observational study.)
- Acute appendicitis remains the most common surgical emergency in pediatrics. Although serum markers are helpful, imaging, in particular point of service ultrasonography and targeted computed tomography (CT), has reduced the false-negative appendectomies to less than 2%. (5) (Strength of evidence C. Observational study.)
- Improved imaging has changed the course of a child with intussusception. Ultrasonography is close to 100% accurate, resulting in much earlier diagnosis. Incidentally, abdominal CT scanning and magnetic resonance imaging (MRI) have demonstrated that minor small bowel to small bowel intussusceptions occur frequently and are self-resolving. (6) (Strength of evidence D. Expert opinion and review of the literature.)
- Gallstones and gallbladder sludge are frequent findings on abdominal ultrasonographic images and may not be the cause of abdominal pain. (8) (Strength of evidence C. Observational study.)

- Cholecystitis has a less specific presentation in children than in adults. Although laboratory tests are helpful, ultrasonography is better than 90% accurate; imaging should be performed in any child with a suggestive history or physical examination findings. (9) (Strength of evidence B. Prospective diagnostic study.)
- Delayed gallbladder ejection demonstrated by HIDA scan may be an uncommon cause of acute abdominal pain in children. However, many children who undergo cholecystectomy for this reason have recurrence of their pain. (10) (Strength of evidence D. Expert opinion and review of the literature.)
- Pancreatitis in children is being diagnosed more frequently than in the past. In most children, the pancreatitis will not become chronic. (11) (Strength of evidence C. Observational study.)
- Ultrasonography is the imaging modality of choice for yielding information about the pancreas and surrounding tissues. However, CT and MRI are superior to ultrasonography for assessing complications of pancreatitis (14) (Strength of evidence C. Observational study.)
- Malrotation almost always occurs in neonates or infants, but it can occur at any age. Half the cases of malrotation require resection, and in those resected, complications, mainly short bowel syndrome, are common. (16) (Strength of evidence C. Observational study.)
- Constipation is the most frequently identified cause of acute abdominal pain in children. Estimates of the overall frequency of constipation in childhood are as high as 29%. Diagnosis is suggested by history and physical examination findings. (3) (Strength of evidence C. Observational study.)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/3/130.supplemental.



Acute Abdominal Pain

Robert D. Baker, MD, PhD

Pediatrics in Review

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1. A 10-year-old boy presents to the emergency department with abdominal pain of 8 hours' duration and vomiting that began approximately 4 hours ago. He has not had any diarrhea. The pain is constant and severe, with no variation. Physical examination reveals a temperature of 100.8°F (38.2°C). Abdominal examination shows marked abdominal tenderness localized over the right lower quadrant. There is obvious rebound tenderness noted. Bowel sounds are absent. Which of the following is the most appropriate imaging study to perform as a next step to confirm the diagnosis in this patient?
   A. Computed tomographic (CT) scan of the abdomen.
   B. Endoscopic retrograde cholangiopancreatography.
   C. Magnetic resonance cholangiopancreatography.
   D. Magnetic resonance imaging (MRI) of the abdomen.
   E. Ultrasonography of the abdomen.
2. A 2-year-old boy presents with intermittent abdominal pain that started approximately 10 hours ago. He has attempted to eat and drink but has had several episodes of vomiting. There is no diarrhea or fever. The pain appears every 15 to 20 minutes and lasts for approximately 1 to 2 minutes. Between episodes the child is in no distress and in fact seems to be playful. Physical examination reveals a playful child with a soft, mildly tender abdomen. As you start to leave the room, the patient screams in pain and once again holds his abdomen. Under which of the following circumstances is immediate surgical intervention indicated as the best management option for this condition?
   A. Failure of morphine to resolve the pain.
   B. Gross blood in the stool.
   C. Patient older than 1 year.
   D. Recurrence of symptoms 10 minutes after a reduction attempt.
   E. The patient is hypotensive and tachycardic.
3. A 10-year-old obese girl has had intermittent colicky right upper quadrant abdominal pain exacerbated by meals for 2 to 3 weeks. There has been intermittent vomiting, but no fever or diarrhea. The patient is healthy, has no underlying chronic medical problems, and is taking no medications. Abdominal ultrasonography shows multiple shadows in the gallbladder. Which of the following is the most likely cause of the shadows in the gallbladder of this patient?
   A. Black pigment stones.
   B. Brown pigment stones.
   C. Calcium carbonate stones.
   D. Cholesterol stones.
   E. Clumps of white blood cells.
4. A 12-year-old obese boy with recently diagnosed gallstones presents with fever, vomiting, and severe back pain. There is no dysuria or diarrhea. Examination reveals a child in moderate distress with epigastric abdominal tenderness and back tenderness. His serum lipase level is elevated 4 times above the upper limit of normal, and ultrasonography shows inflammation in the pancreas and a small, radiodense object in the pancreatic duct. Which of the following is the next best step in the management of this patient?

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A. Place a nasogastric tube to low suction and keep the patient nothing by mouth for at least 1 week.
B. Restrict intravenous fluids to two-thirds maintenance rate.
C. Start broad spectrum antibiotics to provide gram-negative coverage.
D. Start the patient on a diet high in fats within 24 hours.
E. Treat the pain with frequent doses of morphine.

5. A 3-week-old boy is brought to the emergency department with abdominal pain and distention that began 4 hours earlier. He has had several episodes of bilious vomiting. There is no diarrhea. On physical examination, his abdomen is distended and quite tender. He is in obvious distress. Which of the following is the imaging study of choice to confirm the most likely diagnosis in this patient?

A. Contrast upper gastrointestinal series.
B. CT of the abdomen.
C. MRI of the abdomen.
D. Plain abdominal radiograph.
E. Ultrasonography of the abdomen.

Index of Suspicion

1 Hemoptysis, Hypoxia, and Anemia in a 10-year-old Girl

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Tarchichi and Lupo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-year-old premenarchal girl with a history of chromosome 16 short arm duplication, seizures, and global developmental delay is transferred to us from another hospital for evaluation of new-onset severe anemia, hypoxia, and hemoptysis. At an outside hospital, her heart rate was 140 beats/min, blood pressure was 160/80 mm Hg, and oxygen saturation level was 88% on room air (100% on nonrebreather oxygen supplementation), and she was afebrile. There was no obvious bleeding source on examination. Laboratory evaluation revealed a hemoglobin level of 6.4 g/dL (64 g/L) compared with 13.2 g/dL (132 g/L) 3 years earlier. Chest radiography revealed bilateral diffuse infiltrates. She was transferred to our hospital.

On admission to our hospital, the patient's mother reports that the patient is acting more aggressive than usual and appears pale. Two weeks before admission she had a brief episode of mild upper respiratory tract symptoms without fever. The review of systems is otherwise negative, including no history of weight loss, hematochezia, black tarry stool, epistaxis, bruising/bleeding, scleral icterus, jaundice, or hematuria.

Vital signs on hospital admission are as follows: temperature, 98.8°F (37.1°C); heart rate, 98 to 137 beats/min; respiratory rate, 22 to 36 breaths/min; and blood pressure, 96 to 120/47 to 89 mm Hg. Her oxygen saturation level is 80% on room air and increases to 100% on 100% nonrebreather mask. She is not in distress and is nonverbal but follows commands (consistent with her baseline). Her conjunctivae are pale, and she has poor inspiratory effort without wheezes, rales, or rhonchi. The physical examination results are otherwise normal.

Laboratory studies, imaging, and bronchoalveolar lavage help with the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/3/140.

DISCUSSION

Our patient's laboratory studies revealed a hemoglobin level of 5.1 g/dL (51 g/L), a mean corpuscular volume of 62.2 fL, a serum iron level of 20 μg/dL (3.6 μmol/L), a total iron-binding capacity of 409 μg/dL (73.2 μmol/L), iron saturation of 5%, a transferrin level of 292 mg/dL (35.9 μmol/L), a haptoglobin level less than 15 mg/dL (150 mg/L), a lactate dehydrogenase level of 416 U/L (6.9 μkat/L), and a reticulocyte count of 2.6%. Stool guaiac test results were negative. Urinalysis did not show red blood cells, and the peripheral smear did not show evidence of hemolysis. Endoscopy and colonoscopy showed no signs of bleeding. Our patient's radiograph revealed patchy airspace opacities throughout both lungs, with no evidence of pneumothorax or pleural effusion (Fig 1). Bronchoalveolar lavage showed 270 white blood cells, 39,250 red blood cells, and hemosiderin-laden macrophages. Owing to concern for vasculitis or systemic illness, the patient underwent lung biopsy, and the lung grossly was found to be diffusely hemorrhagic and quite dark in color. The final pathologic diagnosis was idiopathic pulmonary hemosiderosis (IPH).

The Condition

Idiopathic pulmonary hemosiderosis is an uncommon cause of alveolar hemorrhage. (1)(2)(3) It is classically defined by hemoptysis, diffuse parenchymal infiltrates on chest radiography, and iron deficiency anemia. (1)(2)(4) The degree of anemia varies with the amount of hemorrhage, and the clinical presentation can be variable. The incidence is approximately 0.24 to 1.23 per million. The etiology of IPH is not fully understood. (1)(2) Many authors believe that IPH likely occurs in genetically predisposed individuals and is triggered by an event, such as an infection. (1)(5) *Stachybotrys* has been linked to a cluster of patients with IPH in Cleveland, but this association was not established. (1) Nuesslein et al (1) stated, "When any bleeding occurs from alveolar capillaries into pulmonary tissue, hemoglobin will be transformed to hemosiderin. Hemosiderin is ingested by macrophages, which will then produce pro-inflammatory molecules leading to chronic inflammation and fibrosis if bleeding occurs repeatedly." Idiopathic pulmonary hemosiderosis is more common in children than adults and typically occurs in children younger than 10 years (mean age, 4 years). (1)(2)(5) Historically, the median survival rate has been 3 to 5 years from the time of diagnosis. (4) Most experts now believe that early diagnosis and aggressive immunosuppression can significantly prolong survival. (1)(2)

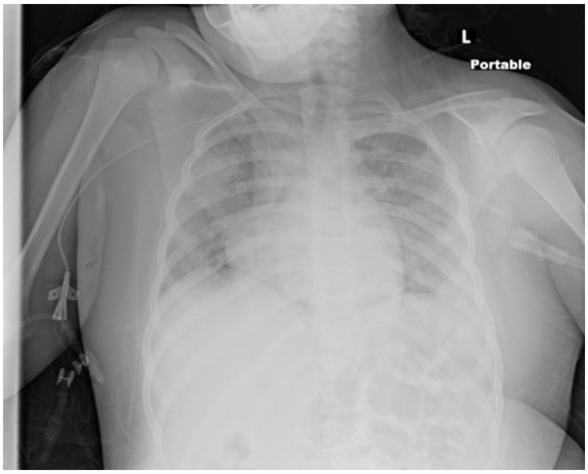

Figure 1. Chest radiograph shows airspace opacities in both lungs.

Idiopathic pulmonary hemosiderosis has been associated with celiac disease, an autoimmune disorder. This association is known as the Lane-Hamilton syndrome, and there are numerous cases described in the literature. (6)(7) It is also reported that 1 of 4 children with IPH will develop an immune disorder later in life. (2) Conditions that can present similarly to IPH are Goodpasture syndrome and Heiner syndrome (primary hemosiderosis with cow milk hypersensitivity). (1) However, Goodpasture syndrome is associated with acute kidney injury usually associated with rapidly progressing glomerulonephritis in addition to the hematemesis, anemia, and pulmonary infiltrates. Heiner syndrome is associated with cow milk protein allergy.

Diagnosis

The variability in presentation can make diagnosis challenging. In their 1999 article "Prognosis in Pediatric Idiopathic Pulmonary Hemosiderosis," Saeed et al (2) reported that "all patients diagnosed had anemia and pulmonary infiltrates, 85% had hypoxemia, 65% had hemoptysis, and 70% had fever."

The chest radiograph pattern for IPH is classically described as a "butterfly" or "batwing" pattern, with symmetrical alveolar infiltrates slanting upward toward the lateral chest walls. (1)

When clinically suspected and after ruling out alternative causes of pulmonary hemorrhage, the diagnosis is typically made, with bronchoscopy and bronchoalveolar lavage revealing hemosiderin-laden macrophages. A lung biopsy is not required but can be used to rule out vasculitis or other systemic illness. (2)

Management

Initial treatment of acute IPH is oral prednisone/prednisolone (2 mg/kg per day) and is effective in most patients. High-dose corticosteroids for 6 months followed by long-term low-dose treatment may be beneficial for some patients. (1) If prednisolone is ineffective, second-line treatment is either pulse dose methylprednisolone (30 mg/kg daily for 3 days) or cyclophosphamide (2–3 mg/kg per day). (1) Other immunosuppressive agents, such as azathioprine or chloroquine, have been shown to be beneficial in some patients. (1) These agents are typically added to corticosteroid therapy or used alone if there is a contraindication to corticosteroid treatment. In those who make a complete recovery, the corticosteroids may be tapered and stopped under close follow-up. Some patients require corticosteroid treatment for an indefinite period.

The clinical course of the disease is variable, and alveolar hemorrhage can be recurrent. When this occurs, the severity of pulmonary symptoms can range from blood-tinged sputum to severe and life-threatening hemorrhage requiring transfusion and intubation. If the hemorrhage interferes with airflow, rigid bronchoscopy may be necessary to remove clots. (1) The diffusing capacity of carbon monoxide is a sensitive and useful indicator for monitoring IPH treatment. (8) With treatment, the diffusing capacity of carbon monoxide should return to normal; therefore, elevations can be an indicator of continued or recurrent intrapulmonary hemorrhage. (8)(9)

Owing to a high clinical suspicion for IPH, our patient was started on corticosteroids and showed clinical improvement. After the diagnosis was confirmed on biopsy, the decision was made to continue oral prednisone indefinitely. She has had no recurrences, and her respiratory status remains stable.

Lessons for the Clinician

- Idiopathic pulmonary hemosiderosis classically presents as a clinical triad of diffuse pulmonary parenchymal infiltrates on chest radiography, iron deficiency anemia, and hemoptysis.
- Bronchoalveolar lavage positive for hemosiderin-laden macrophages is typically sufficient for diagnosis; however, in rare cases, lung biopsy may be required to rule out other systemic illness as the cause.
- Survival has significantly improved with timely diagnosis, treatment, and monitoring.

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Index of Suspicion

2 Rapid Growth and Abnormal Menstrual Bleeding in a 17-year-old Girl

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AUTHOR DISCLOSURE Drs Senguttuvan, Chin, Elrokhsi, and Wheeler have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl presents for concerns of growing too fast and having continuous menstrual bleeding for the past 4 months. Per her adoptive mother, she has been growing fast since the beginning of adolescence and is continuing to grow taller. Four months before her visit, she began having excessive and continuous menstrual bleeding. She was seen by a gynecologist a month before the current visit and was started on an oral contraceptive pill. However, her menstrual bleeding continues. She reports no visual disturbances, headaches, nausea, vomiting, weakness or numbness in the upper/lower extremities, or galactorrhea. On review of her records, her height has been at greater than the 97th percentile since 11 years of age (Fig 1). Her medical history is significant for mild scoliosis, sleep apnea, and anemia, as well as tonsillectomy and adenoidectomy at 16 years of age. Her social history is complicated by the early death of her biological mother and a history of mental illness in both biological parents.

Her vital signs are as follows: heart rate, 76 beats/min; blood pressure, 131/76 mm Hg; and temperature, 97.3°F (36.3°C). Physical examination is remarkable for tall stature (height, >97%; $Z = +3.90$ SD above the mean) and obesity (body mass index >97%, $Z = +2.43$ SD above the mean), coarse facial features, and very large hands and feet. She also has soft puffy palms. No gross visual field defects are noted. Fundus examination results are normal. Results of the remaining neurologic examination are normal.

The patient had brain magnetic resonance imaging (MRI) without contrast performed at an outside institution that reported a sellar mass with suprasellar extension, consistent with either a pituitary macroadenoma versus craniopharyngioma measuring 2.6 × 2.3 × 2.1 cm (Fig 2).

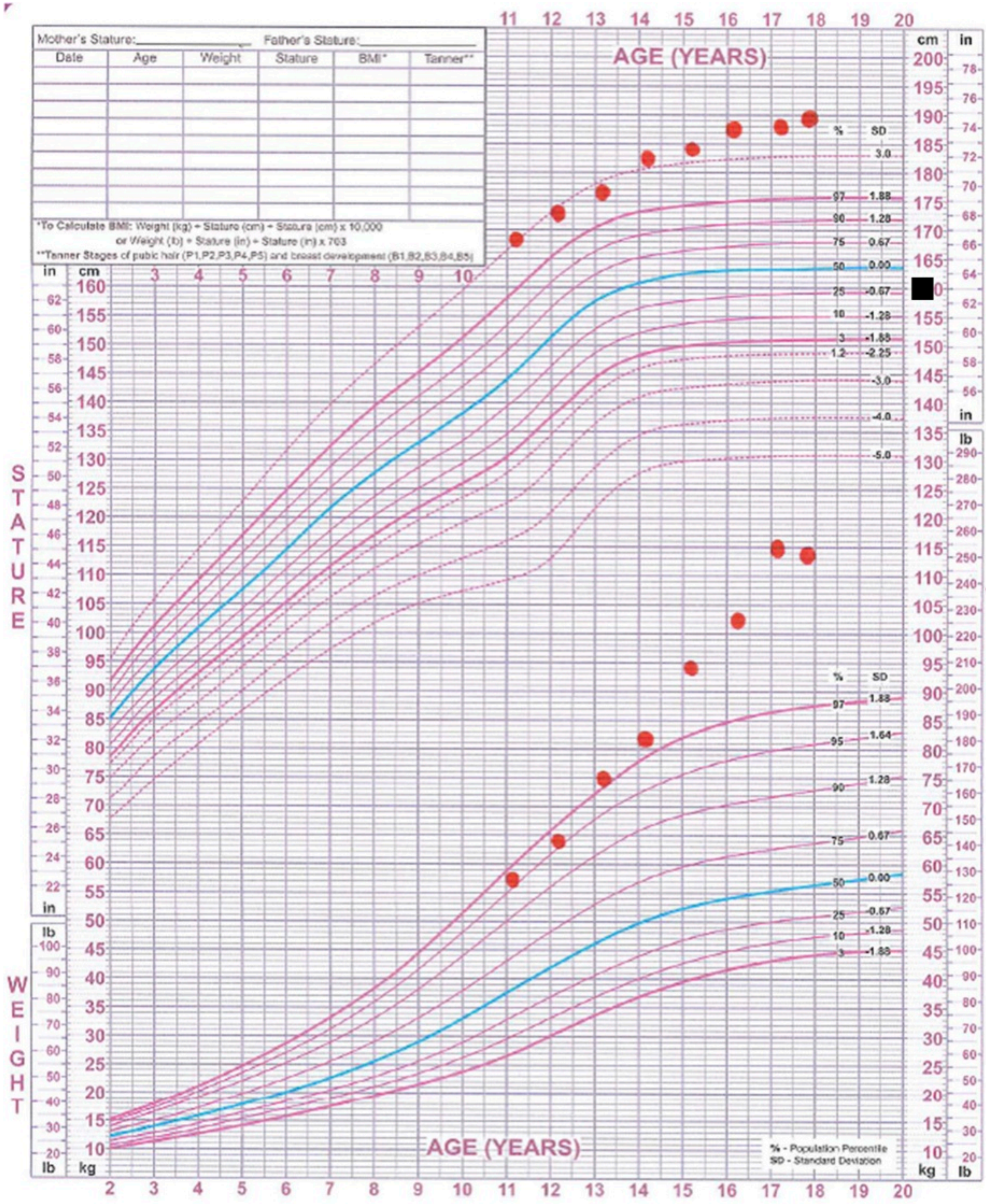

Figure 1. Growth charts show that the height has been at greater than the 97th percentile since 11 years of age and that weight followed the trend after 13 years of age. Black box = mid-parental height.

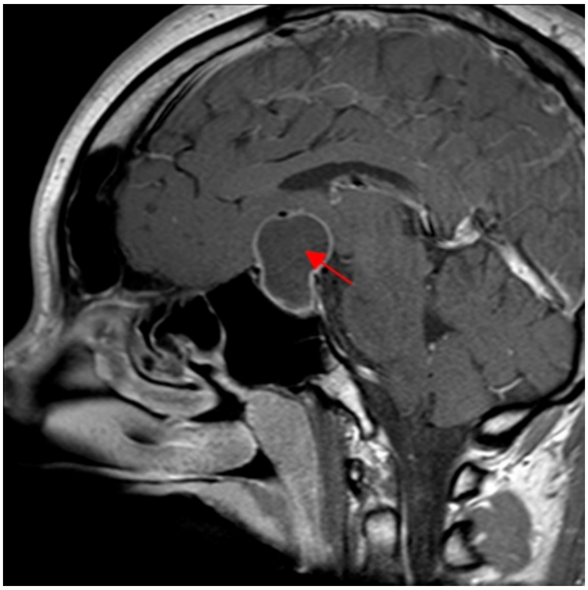

Figure 2. Magnetic resonance image of the brain shows a sellar mass (arrow) with suprasellar extension, consistent with either a pituitary macroadenoma or craniopharyngioma.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/3/141.

DISCUSSION

Laboratory evaluation showed an increased insulinlike growth factor-1 (IGF-1) level of 893 ng/mL (117 nmol/L) (reference range, 268–430 ng/mL [35–56 nmol/L]). A 2-hour oral glucose challenge (75 g of glucose) did not suppress the GH level to less than 1 ng/mL (<1 mg/L). Her serum growth hormone (GH) level was 10.9 ng/mL (10.9 mg/L) (reference range, <1 ng/mL [<1 mg/L]), consistent with GH excess. She also had a low free thyroxine level with a normal thyrotropin level, suggestive of central hypothyroidism. Her prolactin level was increased at 68.4 ng/ml [68.4 μg/L] (reference range, 2.8–26.0 ng/ml [2.8–26 μg/L]). Her cortisol level was 16.2 μg/dL (447 nmol/L) (reference range, 2.3–23.3 μg/dL [63–643 nmol/L]). The luteinizing hormone (<0.1 mIU/mL [<0.1 IU/L]) and follicle-stimulating hormone (FSH) (<0.3 mIU/mL [<0.3 IU/L]) levels were suppressed because she was taking an oral contraceptive pill.

Differential Diagnosis

In children, the differential diagnosis for overgrowth syndromes includes Sotos syndrome, Beckwith-Wiedemann syndrome, Perlman syndrome, Simpson-Golabi-Behmel syndrome, Weaver syndrome, and Marshall-Smith syndrome. The patient's clinical presentation, timing of onset of symptoms, laboratory test results, and brain MRI findings were all consistent with a diagnosis of gigantism caused by GH excess due to the sellar mass.

The Condition

Giants have been a subject of fascination throughout history. From the Biblical accounts of Goliath to the more contemporary Robert Wadlow (Alton giant) and Andre the Giant, giants have been a topic of interest through the ages. Gigantism refers to GH excess that occurs during childhood when the epiphyseal growth plates are open, allowing for excessive linear growth, whereas acromegaly indicates the same phenomenon occurring after epiphyseal growth plate closure.

The incidence of acromegaly is calculated at 3 to 4 cases per million per year, whereas gigantism is extremely rare, with approximately 100 reported cases to date. This is likely an underestimate of the true number. Children with pituitary gigantism have extraordinarily rapid linear growth and are frequently obese. However, the rapid growth in height typically precedes weight gain.

Initial screening tests should include evaluation for pituitary function, including IGF-1 and prolactin levels, as well as screening for visual field defects. The gold standard for diagnosing GH excess is the GH suppression test. Serum GH levels measured 2 hours after a glucose load (1.75 g/kg; maximum, 75 g) fails to suppress to less than 1 ng/mL in cases of GH excess. An MRI of the pituitary gland with contrast is very helpful in locating the source of GH excess.

Management

The 3 therapeutic modalities for pituitary gigantism are surgery, radiation, and pharmacologic therapy. Management of these patients requires a multidisciplinary approach and close follow-up. Pharmacologic therapy includes somatostatin receptor ligands (octreotide, lanreotide) and GH receptor antagonists (pegvisomant).

Ophthalmology evaluation of our patient revealed that she had bitemporal hemianopsia. She was subsequently evaluated by neurosurgery and otolaryngology consultants, and plans were made for surgical excision. The mass was surgically resected via the endonasal route. Her postoperative course was complicated by the development of diabetes insipidus, which presented with large-volume urine output requiring vigorous fluid administration and desmopressin. Histopathology confirmed prolactin- and GH-producing adenoma. Laboratory studies performed 45 days after surgery showed a normal IGF-1 level of 160 ng/mL (21 nmol/L) (reference range, 147–646 ng/mL [19–85 nmol/L]) and a prolactin level of 5.9 ng/ml [5.9 μg/L] (reference range, 4.2–117.9 ng/ml [4.2–117.9 μg/L]). Brain MRI performed 3 months after surgery showed postoperative gliosis and granulation tissue. The patient had irregular menstrual periods due to high prolactin levels. The prolactin levels normalized after surgery, and her menstrual periods became regular at follow-up visits. The patient continues to take desmopressin for diabetes insipidus and levothyroxine for central hypothyroidism and continues to follow up with endocrine, otolaryngology, and neurosurgery specialists.

Lessons for the Clinician

- Children with pituitary gigantism have extraordinarily rapid linear growth and are frequently obese. However, the rapid growth in height typically precedes weight gain.
- Initial screening tests should evaluate for pituitary function, including insulinlike growth factor-1 and prolactin levels. The gold standard for diagnosing growth hormone (GH) excess is the GH suppression test.
- The 3 therapeutic modalities for pituitary gigantism are surgery, radiation, and pharmacologic therapy.
- Clinicians must keep a high level of suspicion for prompt recognition and management of overgrowth syndromes to mitigate the medical and psychological complications of this disease.

NOTE. Portions of this case have been previously published as part of a conference presentation. This case is based on a presentation by Drs Senguttuvan and Elrokhsi at the Endocrine Society's 97th Annual Meeting and Expo, San Diego, California. Poster session: Pediatric Endocrinology, Presentation Date: March 7, 2015 (Poster No. SAT 167).

Suggested Readings

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3 Fever, Vomiting, and Altered Mental Status in a 17-year-old Boy

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AUTHOR DISCLOSURE Drs Pelletier and Bartlett have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old boy with a history of restrictive eating disorder and orthostatic hypotension presents via emergency medical services from an eating disorder facility with 1 week of dizziness and confusion and 1 day of fever. He also reports months of daily first-morning, nonbloody, and nonbilious vomiting.

On presentation to the emergency department he is febrile (temperature, 102.9°F [39.4°C]), tachycardic (heart rate, 112 beats/min), and hypotensive (blood pressure, 91/46 mm Hg) and requires oxygen via nasal cannula. His weight is 114.2 lb (51.8 kg) (3rd percentile), height is 64.6 in (164 cm) (5th percentile), and BMI is 19.3 (15th percentile). General physical examination findings are normal.

Shortly after arrival, the patient develops a brief episode of upper extremity tonic extension, unresponsiveness, and desaturation. He recovers spontaneously without an apparent postictal period. Repeated neurologic examination reveals slowed but appropriate responses to questioning. Cranial nerves, strength, sensation, and reflexes are normal. Upper extremity coordination is normal, but he has right greater than left ataxia with heel-to-shin testing. The patient is unable to stand for gait and Romberg testing due to dizziness.

Laboratory tests before fluid therapy are remarkable for a serum sodium concentration of 149 mEq/L (149 mmol/L) (reference range, 135–145 mEq/L [135–145 mmol/L]), a serum chloride concentration of 118 mEq/L (118 mmol/L) (reference range, 96–108 mEq/L [96–108 mmol/L]), leukocytosis, and normocytic anemia. Urinalysis results are normal, with a urine specific gravity of 1.010. Chest imaging reveals multifocal consolidation concerning for aspiration pneumonia. The patient receives fluids and ceftriaxone. Laboratory studies after fluid therapy reveal worsened hypernatremia and persistently dilute urine. Further testing reveals the underlying diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/3/144.

DISCUSSION

The patient underwent computed tomography of the brain followed by magnetic resonance imaging (MRI) of the brain and total spine, which showed multiple masses in the foramen of Monroe, pineal region, suprasellar region, cervical medullary junction, and left cerebellum (Fig). Serum and urine osmolarity confirmed diabetes insipidus, attributed to loss of pituitary function. Serum cortisol and adrenocorticotropic hormone levels were inappropriately low. Thyrotropin and free thyroxine levels were also low. He was diagnosed as having panhypopituitarism and was managed with vasopressin, hydrocortisone, levothyroxine (after hydrocortisone replacement), and antibiotics. Serum tumor marker levels, including α-fetoprotein (AFP) and human chorionic gonadotropin (HCG), were normal. A lumbar puncture was performed, revealing normal cell counts, cytologic findings, and AFP levels and a minimally elevated HCG level (13 IU/L). Given the combination of multiple midline tumors, panhypopituitarism, and nearly normal tumor markers, the diagnosis of primary central nervous system (CNS) germinoma was suspected. The patient underwent brain biopsy, which confirmed the diagnosis.

Differential Diagnosis

Vomiting is a common complaint among children. The differential diagnosis of vomiting is exceptionally broad and includes etiologies from nearly every organ system. Red flags for intracranial causes of vomiting include 1) first-morning symptoms, 2) positional vomiting, 3) vomiting without nausea, 4) altered mental status, 5) abnormal findings on neurologic examination, 6) seizures, and 7) blood pressure changes out of proportion to illness. (1)

The combination of fever, vomiting, and altered mental status in pediatrics should prompt the clinician to immediately rule out life-threatening etiologies. Such causes include encephalitis, stroke, seizures, CNS abscess or hemorrhage, intoxication or withdrawal, sepsis, electrolyte disturbances, malignancy, uremia, thyroid storm, and CNS vasculitis. Primary CNS tumors represent a small minority of such presentations. (1)(2)

The Condition

Germinomas are a subset of intracranial germ cell tumors, which represent approximately 3% of pediatric CNS tumors. They are related to other nongermanomatous germ cell CNS tumors (NGGCTs), including choriocarcinomas and teratomas. (2)(3)(4)(5) Most patients are 10 to 21 years old at diagnosis, and there is a 3:1 male to female predominance. (2)(3)(4)(5) Tumors are typically found in the midsagittal plane; the most common locations are the pineal gland and the suprasellar area. Other locations, such as the foramen of Monro and the cerebellum, seen in our patient, are less common. (2)(3)(4)(5)

Presentation is variable depending on the tumor location. Tumors in the suprasellar region interrupt axonal projections from the hypothalamus to the pituitary gland and result in

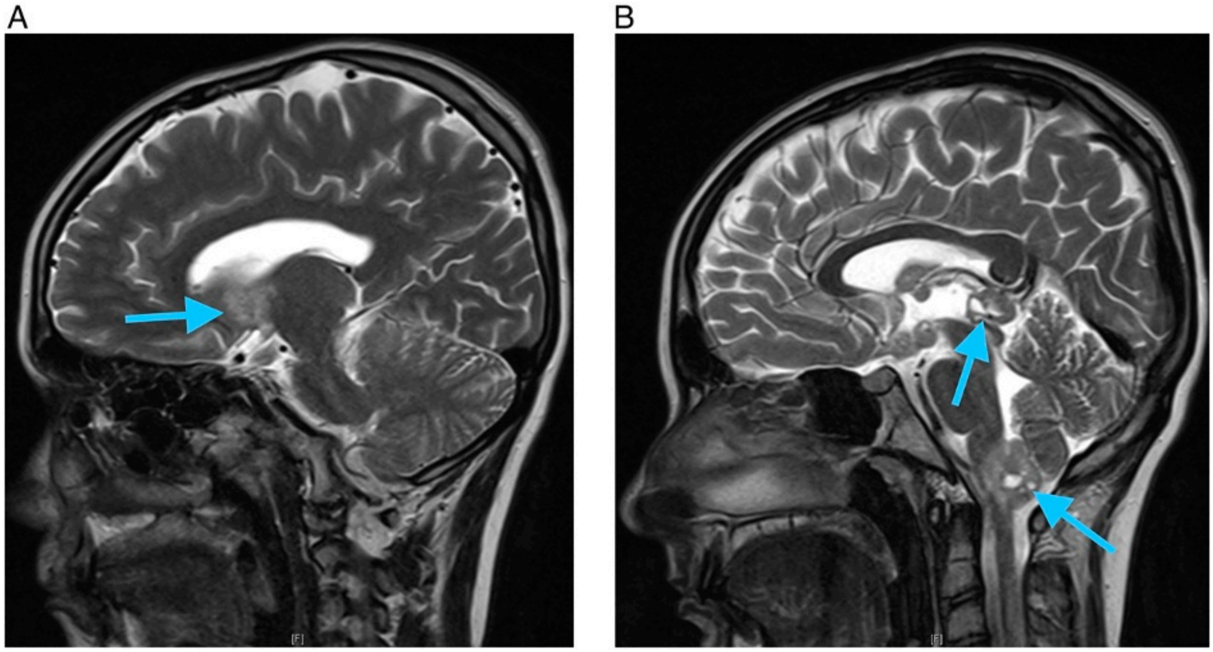

Figure. Sagittal T2-weighted magnetic resonance images show enhancing masses marked by arrows in the (A) suprasellar area, (B) pineal region, and the (B) cervical medullary junction. The patient also had a small left cerebellar mass and a tumor in the foramen of Monroe (not shown). The radiologic differential for multiple midline tumors in a patient this age included pinealoblastoma or germ cell tumor with ependymal spread.

endocrinopathies. Diabetes insipidus is the most common, but larger tumors can present with panhypopituitarism. (2)(3)(4)(5) Tumors in the pineal gland compress the aqueduct of Silvius and can lead to obstructive hydrocephalus. Delayed diagnosis is common, especially in patients initially presenting with endocrine symptoms. (2)(3)(4)(5)

Diagnosis

The diagnosis can be suspected based on neuroimaging studies compatible with midline tumors in the characteristic locations, as described previously herein. Tumor markers, including AFP and HCG, are typically nearly normal in germinomas and are often drastically elevated in NGGCTs. Brain biopsy is required for definitive diagnosis. (2)(3)(4)(5) As with other patients with clinical panhypopituitarism, stabilization with hormone replacement is essential. (6) Hydrocortisone should be administered before diagnostic procedures or thyroid hormone replacement to avoid precipitating an adrenal crisis. (6)(7)(8)

Treatment and Prognosis

Patients should undergo MRI of the brain and spine and diagnostic lumbar puncture at the time of diagnosis for staging purposes. Patients with more than 1 site of tumor, positive CSF cytologic findings, or tumors outside of the CNS are considered to have metastatic disease. Germinomas are exquisitely radiosensitive. (9)(10)(11) Patients with metastatic disease universally receive craniospinal radiotherapy; those with localized disease may undergo local radiotherapy. Neoadjuvant chemotherapy with bleomycin, etoposide, and cisplatin or carboplatin may be used. (9)(10)(11) Survival is excellent, with 98% 5-year event-free survival among patients with metastatic germinoma. (12) However, patients receiving craniospinal radiotherapy are at increased risk for a variety of late complications, including vascular disease, stroke, endocrinopathies, and neurocognitive deficits. (13)

Case Follow-up

After treatment for his panhypopituitarism, the patient had a marked improvement in his nausea and vomiting, and his appetite dramatically improved. He gained 17.6 lb (8 kg) during the following 2 weeks, restoring his BMI to the 40th percentile. He began craniospinal radiotherapy and is followed by the oncology and endocrinology services. As of his last clinic visit, he was doing well, endorsing only fatigue. His nausea, vomiting, and orthostasis had completely resolved. Evaluation by pediatric psychiatry revealed that although he endorsed some anxiety around body shape, he denied dieting, calorie counting, or fear of weight gain, and he did not meet the criteria for a restrictive eating disorder.

Lessons for the Clinician

- Red flags for intracranial causes of vomiting include 1) first-morning symptoms, 2) positional vomiting, 3) vomiting without nausea, 4) altered mental status, 5) abnormal findings on neurologic examination, 6) seizures, and 7) blood pressure changes out of proportion to illness.
- Patients with diabetes insipidus often experience delayed diagnosis, and a high index of suspicion must be maintained. The condition can be suspected based on the low specific gravity of routine urinalysis combined with hypernatremia on serum chemical analysis.
- Primary central nervous system germinomas are a rare cause of panhypopituitarism and obstructive hydrocephalus, most commonly in adolescent boys. Brain biopsy is essential in diagnosis. Radiotherapy is the mainstay of treatment, and the prognosis is excellent.

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4

A Patterned Acute Skin Lesion on a Leg of a 17-month-old Boy

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AUTHOR DISCLOSURE Drs Kellogg, Northrop, and Browning have disclosed no financial relationships relevant to this article. Dr Northrop's current affiliation is Wake Forest Baptist Health, Winston-Salem, NC. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-month-old previously healthy boy presents to the emergency department with an unexplained skin lesion on his right leg. The mother reports seeing the lesion a few hours ago when the child returned home from a 2-day visit with his father. She says the father noted the mark 2 days earlier, and asked her if the child was allergic to socks. The parents have been separated since the child's birth and share custody of their son. The treating physician notes a "bright red lesion" on the right leg posteriorly that is "sharply marginated," photographs the lesion (Fig), and documents the lesion as suspicious for "nonaccidental trauma with an electric cord." A report is made to Child Protective Services. However, the child does not undergo evaluation for abuse.

A child abuse specialist sees the child 3 days later. The mother indicates that the child had stated that his father hit him. The mother states that her son at 2 months of age had a similar, yet more proximal mark on the same leg, and she produces photographs taken at the time that her son's previous lesion appeared. A physician examined the infant about 1 week after the first lesion appeared, but the physician was unable to determine a cause. The lesion resolved spontaneously over a few weeks.

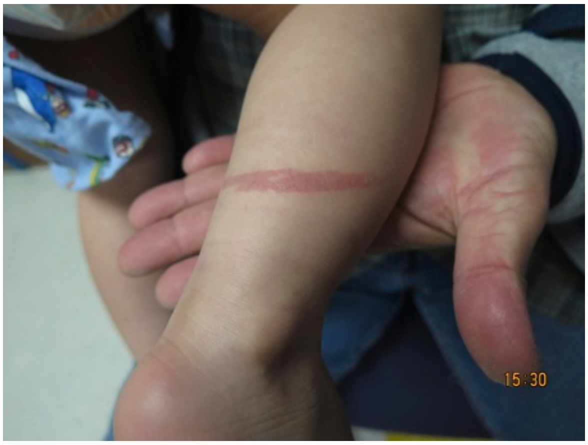

Figure. An erythematous, slightly raised lesion is seen on the posterior aspect of the right leg.

The child has no previous hospitalizations but is allergic and/or sensitive to several substances, including turkey, milk, gluten, human milk, soaps, and detergents. He is currently taking amoxicillin and a nonprescription cough medicine for bronchitis.

On examination by the child abuse specialist, the lesion appears unchanged compared with photographs taken 3 days previously; the lesion is erythematous, slightly raised to palpation, with small vertical hatch marks noted medially, and is seen on the posterior aspect of right leg (Fig). The remainder of his examination findings are completely normal.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/3/145.

DISCUSSION

Additional information was obtained from the father by telephone after the clinic visit. During the first incident at age 2 months, the father confirmed that the infant was wearing an infant garment with pant legs. The mother was caring for the infant when the first lesion was observed. The second and current skin lesion was noted by the father 1 to 2 hours after the patient wore new unwashed toddler-sized socks made of polyester, spandex, rubber, and nylon. The child abuse specialist referred the child to a dermatologist 5 days after the second lesion appeared. A biopsy of the lesion was nonspecific, and only lymphocytes were visualized, with no evidence of thermal injury or allergic contact dermatitis. Three weeks later, the child developed another similar red curvilinear lesion on the anterior part of the right leg 1 to 2 hours after wearing washed cotton blend socks.

THE CONDITION

Infantile garment bands, or sock line bands, are considered a rare condition, with approximately 20 cases, mostly involving infants, described in the literature. Previous case reports have indicated tight garment bands/elastics as the most likely cause for these lesions, although some reports have mentioned factors such as dermal inflammation and panniculitis, dermatographism, and activation of mast cells. The band lines described are typically continuous, partially circumferential, and involve the posterior region of legs, although some bands occurred on the thighs and wrists. Other reported characteristics of sock line bands included blistering focal desquamation, hyperpigmentation, and bilaterality. Comorbid conditions were not commonly present, although some children had eczema. None of the publications have described recurrent sock line bands. The bands may occur from pressure-induced irritation of the skin. The tightness causes constriction of the epidermis, and this leads to irritation and inflammation, resulting in erythema. Postinflammatory hyperpigmentation occurs in some cases and can persist for months or years.

It is surprising that the condition is considered rare. We speculate that, in reality, it is not a rare condition but only rarely reported in the medical literature. Imprints from garment bands may present as bright erythematous lines and can persist for months or years.

Based on clinical presentation, examination findings, and biopsy results, the underlying mechanism for the garment bands in this child was undetermined. Although others have reported mast cell degranulation as a possible mechanism, only lymphocytes and no mast cells were seen on biopsy of our patient's lesions. Of interest, related to this case is that all lines occurred on the right calf: 2 were posterior and 1 anterior. In addition, none of the lines were completely circumferential, as may be expected with constriction occurring circumferentially.

DIFFERENTIAL DIAGNOSIS

Patterned injuries, particularly in infants, are highly concerning for physical abuse. When skin lesions are unexplained, the concern for abuse is typically higher, especially if the infant is not yet mobile. Accidental injuries in mobile children tend to be nonpatterned and occur overlying anterior bony prominences.

Dermatologic conditions that may produce distinct patterns that mimic traumatic injuries include phytophotodermatitis and chemical burns. Other conditions that are reported to resemble garment line bands are amniotic bands, acquired raised bands of infancy, pigmentary mosaicism, dermal melanocytosis, linear epidermal nevus, and incontinentia pigmenta. Although acquired raised bands of infancy are associated with swelling and discoloration at the line of elasticized sock tops, infants with this condition typically have dermatographism from birth and recurrent episodes of cutaneous whealing; some also have congenital constriction bands. In contrast to garment bands, acquired raised bands of infancy become progressively palpable after the redness fades and biopsy shows an infiltrate of adipocytes along capillaries in the upper dermis. Raised bands of infancy are more often skin colored, asymmetrical, and persistent; can be progressive; and are typically associated with limb defects. A similar condition, congenital curvilinear palpable hyperpigmentation, has been described but is thought by some to be sock line bands.

In this case, the lesion did not change in appearance over 4 days but resolved within a few weeks. A thin line of hyperpigmentation persisted for 3 months after the first episode of garment band but was not seen after the 2 subsequent lesions.

MANAGEMENT AND PROGNOSIS

There is no specific treatment for garment bands. Most lesions resolve without any permanent skin scarring or pigmentary abnormalities.

Lessons for the Clinician

- Although patterned lesions resembling injuries in young children and infants are generally concerning for abuse, the clinician may consider other nontraumatic causes for such lesions

- Photodocumentation over time can be useful in differentiating traumatic and nontraumatic causes of skin lesions.

Suggested Readings

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5

Headache, Vomiting, and Elevated Blood Pressure while Voiding in an 8-year-old Girl

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AUTHOR DISCLOSURE Drs Healey, Fardy, and Chan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 8-year-old girl from South Sudan presents to the emergency department with a history of severe headache and vomiting with urination. She describes the headache as being present "all over" her head and rates the pain "15/10." There is no history of morning or positional headache. She has had a history of vomiting with urination and defecation since she was 1 year old. From 1 to 6 years of age, the vomiting occurred sporadically, but during the 2 years before the emergency department visit, vomiting was occurring 4 to 5 times daily with voiding and defecation.

Initial vital signs reveal a heart rate of 114 beats/min, a respiratory rate of 24 breaths/min, a temperature of 97.0°F (36.1°C), and blood pressure (BP) of 122/88 mm Hg. Funduscopic examination results are normal. Results of cardiovascular, respiratory, abdominal, and central nervous system examinations are normal.

In the emergency department, we observe the child screaming with a headache and vomiting after 3 separate voids. Her BP increases to 143/94 mm Hg during these episodes. Between voids, she does not complain of headache and does not vomit. Her headache is treated with intravenous morphine. After treatment with morphine, the BP returns to 120/84 mm Hg. We provide no further treatment for hypertension in the emergency department. She is hospitalized. Further review of the history and testing lead to the diagnosis.

The Case Discussion appears with the online version of this article at http://pedsinreview.aappublications.org/content/39/3/147.

DISCUSSION

The review of medical records from previous clinic visits showed that she had been consistently hypertensive during the previous 2 years, with BPs ranging from 105/65 to 126/70 mm Hg (for her height and age, 50th percentile BP is 99/59 mm Hg, stage 1 hypertension is 116/77–123/84 mm Hg, and stage 2 hypertension is >123/84 mm Hg). Her elevated BPs were not observed on multiple clinic visits. She has no history of excessive sweating but did complain of occasional palpitations in the 6 months before presentation to the emergency department.

The initial differential diagnosis included brain tumor, essential hypertension, benign intracranial hypertension, and pheochromocytoma.

On laboratory evaluation, the complete blood cell count; blood urea nitrogen, creatinine, electrolyte, glucose, thyrotropin, and morning cortisol levels; and urinalysis results were all normal. Findings from a computed tomographic (CT) scan of the head were also normal. Abdominal ultrasonography revealed the presence of a bladder mass (Fig 1). Abdominal magnetic resonance imaging confirmed the presence of a lobulated, heterogeneous, well-defined lesion measuring 3.9 × 3.1 × 3.3 cm in the superior aspect of the bladder (Fig 2). Studies on a 24-hour collected urine sample showed a significantly elevated norepinephrine level of 77.5 pg/ml (13,111,600 pmol/L; reference range, 0.93–4.68 pg/ml). Her plasma norepinephrine level was also elevated at 0.130 pg/ml (22,000 pmol/L; reference range, <0.005 pg/ml). Based on the clinical and biochemical picture, a diagnosis of bladder paraganglioma was made.

The patient was referred to the surgical team for resection of the paraganglioma. She was prepared for surgery initially with phenoxybenzamine, with atenolol added after adequate α-blockade was achieved. With a 3-week period of treatment, her BP normalized to 106/58 mm Hg. She then underwent transvesical resection of the tumor, with partial resection of the bladder cuff. Her BP remained normal after surgery. One month after surgery, the patient had a normal BP and no recurrence of symptoms.

Results of the genetic studies for both von Hippel-Lindau *(VHL)* and succinate dehydrogenase *(SDH)* gene mutations were negative.

The Condition

Paragangliomas are neuroendocrine tumors that arise from neural crest–derived cells or organs. They develop along the sympathetic and parasympathetic ganglia, particularly the carotid body, jugular foramen, mediastinum, organ of Zükerkandl, and periaortic region. These tumors are rare, with an incidence of less than 0.3 cases per million per year. Between 10% and 20% of cases are diagnosed in the pediatric population. Overall, paragangliomas account for 1% of pediatric patients with hypertension.

Most paragangliomas are hormonally active, producing excessive amounts of catecholamines that are responsible for the symptoms seen in many patients at the time of diagnosis (Table). Bladder paragangliomas may present with hematuria or paroxysmal symptoms during voiding in 50% of patients due to involvement of the detrusor muscle.

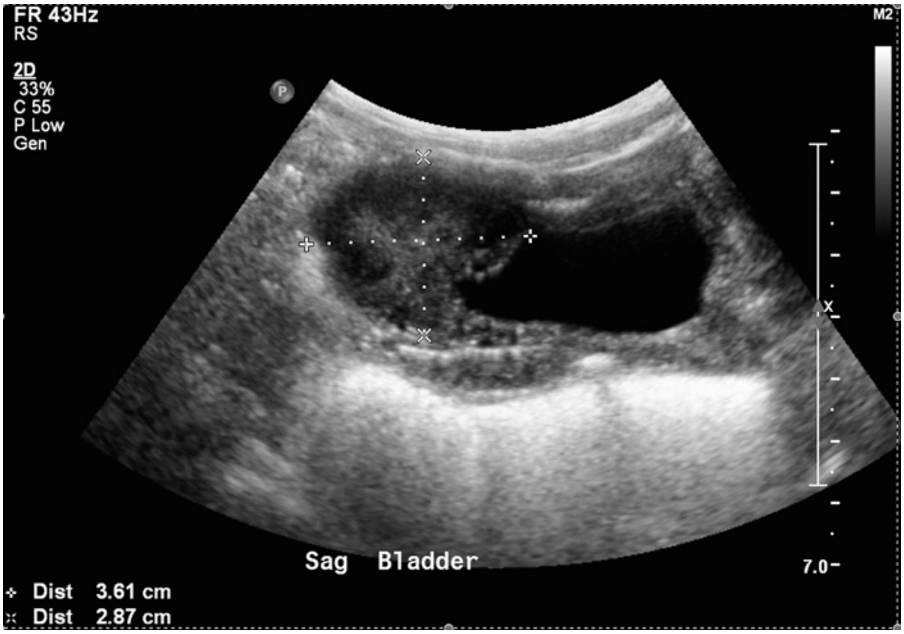

Figure 1. Abdominal ultrasonography shows a mass in the urinary bladder.

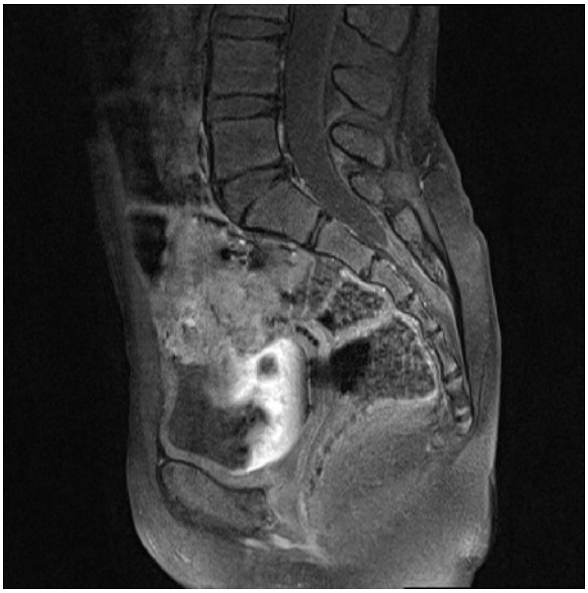

Figure 2. Abdominal magnetic resonance imaging shows the presence of a lobulated, heterogeneous, well-defined lesion measuring 3.9 × 3.1 × 3.3 cm in the superior aspect of the bladder.

The first step in the diagnosis of a paraganglioma is to confirm excessive catecholamine production by measurement of plasma or urine levels. Measurement of fractionated plasma metanephrine levels has sensitivity near 100% but specificity of 85%. The sample must be collected while the patient is supine because false-positive results may occur in the sitting position. A 24-hour urinary metanephrine test has sensitivity of 88% and specificity of 99.7%. Collection is time-consuming, and urine must be collected during a crisis or immediately afterward. A CT scan or a magnetic resonance image is then used to localize the tumor(s). Functional imaging, including metaiodobenzylguanidine or positron emission tomography, is highly specific and can confirm the catecholamine-secreting nature of the tumor. It also can be used to localize tumors not seen with cross-sectional imaging and identify other sites of disease.

TABLE. Signs and Symptoms of Paraganglioma in Children

CLASSIC	NONSPECIFIC
Hypertension	Blurred vision
Paroxysmal episodes	Hyperglycemia
• Headache	Gastrointestinal symptoms
• Palpitations	Weight loss
• Diaphoresis	Polyuria
Pallor	Polydipsia
Orthostatic hypotension	Low-grade fever
Syncope	Behavioral changes
Tremor	
Anxiety	

Surgical resection is the definitive treatment for a paraganglioma. Before surgery, it is crucial to achieve adequate α_1-adrenergic blockade with an agent such as phenoxybenzamine to minimize intraoperative BP elevation due to catecholamine surges that may occur due to surgical manipulation of the tumor. Once adequate α-blockade is obtained, a β-blocker may be added to prevent reflex tachycardia. If β-blockade is added too early, a hypertensive crisis can result from significant unopposed α-mediated vasoconstriction. Medical preparation for surgery may take several weeks. In addition, the patient should be salt-loaded a few days before surgery to expand blood volume and minimize postoperative hypotension.

Between 40% and 59% of childhood paragangliomas are due to genetic mutations, including *VHL*, *SDH*, neurofibromatosis 1 *(NF1)*, and rearranged during transfection *(RET)* proto-oncogene germline mutations. Consultation with a geneticist to arrange genetic testing is, therefore, recommended for all children presenting with paragangliomas. Approximately 12% of pediatric paragangliomas are malignant. Risk factors for malignancy include extra-adrenal location, size greater than 6 cm, and sporadic occurrence.

The prognosis for a surgically resected paraganglioma is excellent if the lesion is benign. However, these tumors can sometimes have unpredictable clinical behavior and metastasize late in the clinical course, and, therefore, long-term follow-up with measurement of plasma or urine metanephrine levels and imaging studies is required.

Lessons for the Clinician

- Vomiting and headaches may be the presenting symptoms for elevated blood pressure in children.
- Catecholamine-secreting tumors should be considered in the differential diagnosis of hypertension in children.
- Symptoms of catecholamine excess may occur only during micturition if the tumor is located in the bladder.
- Plasma metanephrine level is the test of choice to confirm catecholamine excess.
- Children with paragangliomas should undergo testing for underlying mutations in the *VHL* or *SDH* genes.

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6

Abdominal Distention and Constipation in a 70-day-old Female Infant

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AUTHOR DISCLOSURE Drs Lancaster, Lear, Brant, Riedel, and Minardi have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 70-day-old female infant presents to the emergency department (ED) with a 1-month history of abdominal distention and constipation. The patient was born at term via vaginal delivery. She is formula fed with a cow milk protein formula and routinely consumes 4 oz every 4 hours. She passed meconium within 24 hours after birth. However, since that time she has not stooled regularly, and her parents have administered daily diluted fruit juices and enemas every other day to promote defecation. Despite these interventions, her abdomen has become more distended, and the parents report that her constipation continues.

In the ED her vital signs are temperature 98.6°F (37.0°C), blood pressure 111/62 mm Hg, pulse 137 beats/min, respiratory rate 22 breaths/min, and oxygen saturation 100% on room air. Her examination shows a well-appearing baby in no apparent distress. Her cardiopulmonary examination findings are normal. Extremity examination shows capillary refill within 2 seconds, and there is no appreciable edema. Peripheral pulses are strong. The patient's abdomen is distended but nontender and without any cutaneous findings suggesting portal hypertension. Bedside abdominal ultrasonography performed by the ED physician demonstrates ascites without any organomegaly (Fig 1). She is admitted to the pediatric service at that time.

Results of laboratory studies are largely normal (aspartate aminotransferase, alanine aminotransferase, albumin, electrolyte panel, and lipase) except for peripheral eosinophilia noted on the complete blood cell count (white blood cell count, 10,500/μL [10.5×10^9/L]; eosinophils, 15%; absolute eosinophil count, 1.5×10^9/L). The total serum immunoglobulin E (IgE) level is normal at 3.36 mg/L. An echocardiogram is obtained that reveals normal cardiac function and anatomy. Consultative ultrasonography is completed, again demonstrating uncomplicated ascites. The patient is sent to the interventional radiology service for image-guided sampling of the ascitic fluid. Twenty milliliters of milky white fluid is removed

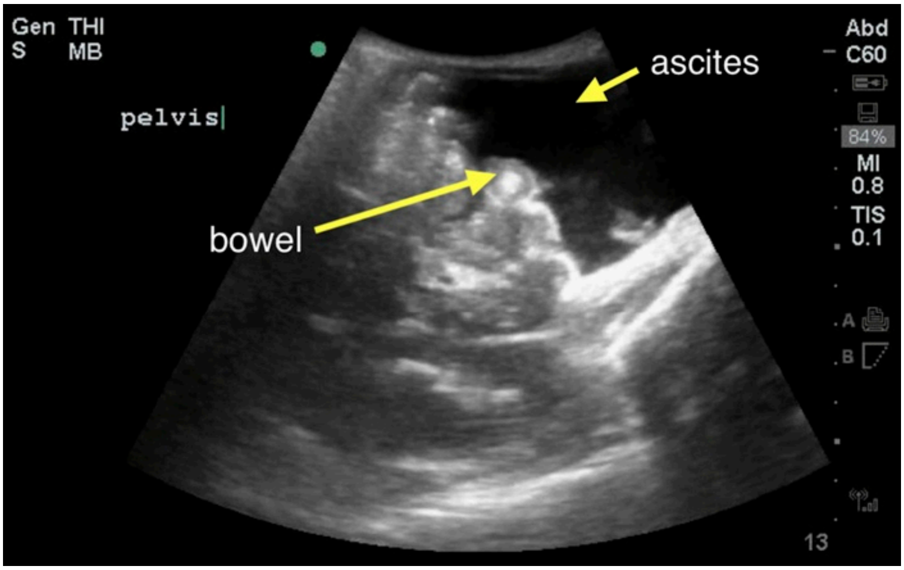

Figure 1. Ascites is seen in the pelvis surrounding multiple intestinal loops.

from the abdomen and sent to the laboratory, which verifies a triglyceride-rich fluid consistent with chylous ascites (CA) (fluid triglyceride level, 3,509 mg/dL [40 mmol/L]).

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/3/148.

DISCUSSION

Due to the findings of CA and peripheral eosinophilia, milk protein allergy was suspected, and the patient was changed to an elemental formula. Despite changing formula, the patient continued to have worsening eosinophilia (25%). She was taken to the endoscopy suite, where an esophagogastroduodenoscopy was performed showing patchy gastric and duodenal erythema, and a flexible sigmoidoscopy was performed and had normal findings. Mucosal biopsies of samples taken from this tissue revealed eosinophilic infiltration of the lamina propria of the stomach and duodenum, focally in numbers as great as 25 per high-power field, including prominent eosinophil degranulation (Fig 2). The villous architecture of the duodenum was normal. The rectosigmoid biopsy showed rare eosinophilic cryptitis and occasional stromal eosinophils. In the clinical context, the pathology results were strongly supportive of eosinophilic gastroenteritis (EG), likely due to milk protein allergy.

Per Cárdenas and Chopra (1), "Chylous ascites is the accumulation of a milk-like peritoneal fluid rich in triglycerides, due to the presence of thoracic or intestinal lymph in the abdominal cavity. It develops when there is disruption of the lymphatic system due to traumatic injury or obstruction (from benign or malignant causes)." In this patient there is an absence of a major lymphatic malformation, trauma, or recent surgery. Therefore, the most likely explanation for the development of CA is lymphangiectasia due to inflammation caused by EG. Lymphangiectasia can be patchy and challenging to confirm on endoscopic biopsy so its absence in our patient's duodenal biopsy samples does not rule it out. (2) As a result of our patient's subsequent clinical course, we believe that her CA is due to secondary, and not primary, lymphangiectasia.

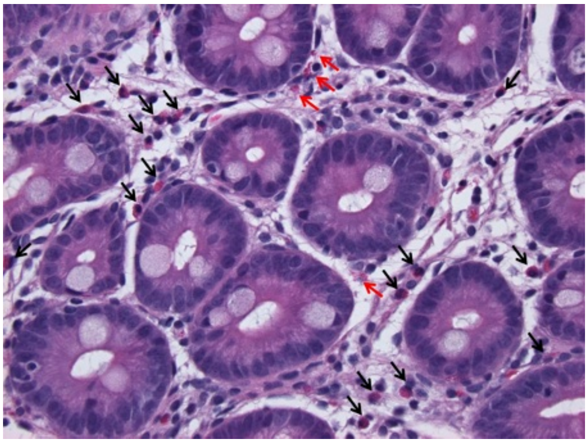

Figure 2. Mucosal biopsy showing eosinophilic infiltration of the lamina propria of the stomach and duodenum (black arrows), focally in numbers as great as 25 per high-power field, including prominent eosinophil degranulation (red arrows).

THE CONDITION

Eosinophilic gastroenteritis is a term used to describe one of the eosinophilic gastrointestinal disorders, which also include eosinophilic esophagitis, gastritis, enteritis, and colitis. Eosinophilic gastroenteritis is a rare inflammatory disease in children that manifests by infiltration of eosinophils in the gastric and small-bowel mucosa without other known cause of eosinophilia. Although there are limited data on the prevalence of EG, it is estimated to affect 22 to 28 per 100,000 people in the United States. (3)

The pathogenesis of EG is poorly understood, but it seems that there is likely an allergic component to the disease because elemental or elimination diets often improve symptoms, according to several reports. (4) In addition, most children with EG also have an increased serum IgE level. In patients with allergic EG, a population of interleukin 5–expressing food allergen–specific T-helper 2 (Th2) cells has been identified. (5) It is theorized that food exposure activates these Th2 cells, which then release chemokines (specifically, eotaxins), which lead to recruitment of eosinophils to the gut. (6) Once present, eosinophils induce local inflammatory change by 2 mechanisms. First, eosinophils mediate a proinflammatory effect through the release of cytokines, chemokines, and lipid mediators. Second, eosinophils induce tissue damage directly through the release of toxic mediators such as major basic protein and eosinophilic cationic protein. (7)(8)

The clinical presentation of EG varies, depending on the location in the gastrointestinal tract and the extent of eosinophilic infiltration in the layers of the affected region. In mucosal disease, the presentation is nonspecific and is most related to location in the gastrointestinal tract. Most commonly, these patients' manifestations include abdominal pain, nausea, vomiting, early satiety, and diarrhea. Malabsorption and failure to thrive are uncommon presentations that can occur in patients with extensive small-bowel disease. In patients with eosinophilic infiltration of the muscular layers (muscularis form), symptoms consistent with wall thickening and impaired motility predominate. These findings can be similar to symptoms associated with intestinal obstruction, including bilious vomiting and abdominal distention. Last, patients with involvement of the serosal layer can present with either isolated ascites or in combination with any of the symptoms noted previously herein in less infiltrative disease. (9) The ascites in such individuals typically contains a high eosinophil count (not present in this case), reflecting exudative cell loss via an inflamed serosal surface (in contrast to the triglyceride chylous fluid found in this case). Of note, patients with serosal infiltration typically demonstrate a higher level of peripheral eosinophilia.

The differential diagnosis of EG includes intestinal parasites, malignancy, Crohn disease, hypereosinophilic syndrome, Langerhans cell histiocytosis, and other uncommon conditions that are usually distinguished from EG on the basis of clinical context and, when necessary, focused diagnostic tests.

The natural history of EG is highly variable and not well characterized. Some other allergic gastrointestinal disorders, such as infant dietary protein–induced enterocolitis and food protein–induced enterocolitis syndrome, typically resolve completely with age. However, based on small case series to date, EG is thought to generally follow a more chronic, persistent course, with periodic symptomatic flares in some affected individuals.

Chylous ascites occurs with the leakage of the milky-white, triglyceride-rich fluid into the peritoneal space. (10) Patients with CA present primarily with massive abdominal distention. In children, causes of CA include lymphatic anomalies, trauma, recent surgery, malignancy, and mycobacterial infection. The most common lymphatic anomaly that causes CA in children is intestinal lymphangiectasia, which is characterized by the dilation of subserosal enteric lymphatic. (11) This lymphatic obstruction can occur anywhere that lymph drainage takes place but favors the pulmonary and gastrointestinal systems. With obstruction of lymphatic vessels, lymph begins to flow into the pleural or peritoneal spaces. In the pleural space, this creates chylothorax, and in the peritoneal space, CA. (12) Lymphangiectasia can be a primary disorder or due to a secondary process that causes lymphatic obstruction. Secondary intestinal lymphangiectasia (SIL) is most commonly caused by congenital heart disease. (12) In our patient, SIL was likely due to gut inflammation obstructing the intestinal lymphatic drainage. Other causes include tuberculosis, Crohn disease, intestinal lymphoma, constrictive pericarditis, and more. (13) Also, SIL can be triggered by focal or diffuse bowel wall thickening, which may be caused by inflammatory processes, including gastroenteritis. (12)

DIAGNOSIS

Due to the nonspecific symptoms associated with EG, physicians must maintain a high index of suspicion in any patient with abdominal complaints and peripheral blood eosinophilia. (14) The latter is observed in more than two-thirds of patients with EG. Presently, there is no noninvasive way to definitively diagnose EG, and endoscopy with biopsy remains the gold standard for diagnosis. (15) Biopsy often shows patchy eosinophilic infiltration of the gut wall and may reveal eosinophils in the crypts or villi. There are no established biopsy criteria for numbers of eosinophils necessary to make the diagnosis of EG, so the overall clinical context and subsequent course remain important contributors to the diagnosis. (16) Patients with ascites due to serosal involvement may undergo diagnostic paracentesis. (14) In patients whose food allergy is not known, skin prick tests and serum food-IgE levels can be used with varying success due to multiple immune responses involved in the disease process. (15)

Ascites must first be confirmed through imaging. (10) Ultrasonography seems to be the best imaging modality for the initial detection of ascites, especially in pediatric patients. Increasingly, ultrasonography may be performed by treating clinicians at the point of care, which may allow an earlier, more accurate diagnosis. (17)(18) Next, a sample of the fluid must be obtained. To diagnose CA, the fluid must have a triglyceride level greater than 200 mg/dL (>2.3 mmol/L) and a total protein level greater than 2.5 g/dL (25 g/L). (2) Elevated central venous pressure can cause lymphatic obstruction, which can trigger lymphangiectasia and CA. In infants this can develop from cardiac anomalies and must be ruled out by a transthoracic echocardiogram. (19) Patients suspected of having CA due to SIL can be diagnosed by imaging, pathology, or both. Abdominal computed tomography with contrast and noncontrast magnetic resonance lymphangiography have been used to make the diagnosis. On endoscopic biopsy, intestinal villi may appear cream-colored and edematous. Dilated lymphatic vessels may also be present. (12) Most often, SIL occurs in the jejunoileum, which can be out of reach of upper and lower endoscopy. As a result, endoscopy for SIL can often appear normal with no signs of dilated lymphatics. Capsule endoscopy has been suggested as the next diagnostic step for a negative endoscopic biopsy and clinical suspicion of SIL; however, it is currently not feasible in infants. (2)

MANAGEMENT

Although there is no standardized treatment for EG, a restricted and elemental diet has proved successful for many patients. Restriction requires that the patient eliminate the allergy-causing food from the diet, assuming the food allergen is known. Patients are then started on an elemental diet. For infants, this means starting an amino acid–based formula. With the implementation of a restricted and elemental diet, most patients see resolution of symptoms and serum eosinophilia within 3 to 6 weeks. (15) Corticosteroid therapy, which suppresses eosinophilic inflammation, is used only in patients who are refectory to dietary changes (14) because corticosteroids must be given systemically to be effective and carry intrinsic adverse effects.

The first-line treatment for CA due to primary lymphangiectasia is a low-fat diet that is high in medium-chain triglycerides (MCTs). In contrast to long-chain triglycerides, MCTs do not need to be transported through the lymphatic system before reaching the circulation. Instead, MCTs are absorbed directly into the portal venous system. Octreotide is sometimes given as a long-acting somatostatin analog to reduce lymph flow in severe cases. (2) Treatment of SIL usually does not require an MCT diet as it often resolves with successful treatment of the underlying condition. (20) Operative treatment, including drainage and shunting, is attempted only if treatment of the underlying condition (SIL) or diet and medication (primary) fail to resolve the ascites. (10)

PATIENT COURSE

While admitted to the hospital, the infant passed regular stools and did not require further evaluation or treatment for constipation. She was discharged on a commercial elemental formula containing 100% amino acids and 33% of the fat blend as MCT oil. At her 2-month follow-up visit she was doing well, with complete resolution of the eosinophilia and ascites. Based on the prompt and sustained resolution of the CA and peripheral eosinophilia with elemental formula feeding, along with strongly supportive gut mucosal biopsy findings, her diagnosis is considered to be SIL due to inflammation from the EG. The subsequent clinical course of the patient has implied that the CA was not due to primary lymphangiectasia because the patient is now tolerating long-chain triglycerides without recurrence of symptoms.

Lessons for the Clinician

- In infants, a distended abdomen may reflect gaseous bowel loop distention, a mass lesion, or ascites, and imaging may be required to distinguish the cause.
- The nature of ascites, determined by paracentesis, may be critically important in leading to an appropriate diagnosis and management.
- Chylous ascites is an uncommon presentation of eosinophilic gastroenteritis. In patients with ascites and eosinophilia, a food allergy should be considered.
- Secondary intestinal lymphangiectasia is the dilation of lymphatic vessels due to another disease process. It usually resolves with treatment of the underlying problem.
- Ultrasonography is the best initial diagnostic tool to confirm ascites. Physicians trained in performing ultrasonography at the bedside can help expedite patient care. (17)

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Clinical Drug Trials

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AUTHOR DISCLOSURE Dr Mason has disclosed that she is a full-time employee of Bayer Pharmaceuticals. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Have you ever thought about how the drug you prescribe made its way to the shelves of the pharmacy from which it will be dispensed? This process of drug discovery and development—of taking a drug from the laboratory to being available in the marketplace to treat individuals—may take up to 12 years and cost more than a billion dollars. In general, this timeline consists of approximately 5 years of laboratory research in which up to 10,000 potential substances are narrowed down to approximately 250 substances, which are then tested in animals and in vivo, after which time the single selected drug is ready to be tested in humans. Drug discovery is a highly regulated process designed to ensure the utmost safety to those who will use the medication: the ultimate goal is to bring drugs that are safe and effective to the market for individual use.

Once a drug is ready for its first test in humans, it enters the 4 phases of clinical drug development:

Phase 1 is the study of human pharmacology and how the drug of interest is absorbed, metabolized, and excreted. This phase is typically conducted in 20 to 100 healthy volunteers to establish a safe dose range, which allows for maximum benefits with minimum risks. Some drugs, such as those being developed for cancer treatment, are deemed unethical for testing in healthy volunteers because of toxic adverse effects. Such drugs undergo phase 1 testing in patients with the target disease. During phase 1 studies, volunteers are closely monitored for adverse effects. Approximately 70% of experimental drugs move from phase 1 to phase 2.

Phase 2 studies are conducted in a small population of people (several hundred) with the target disease to assess the efficacy of the drug and to monitor for common short-term adverse effects. This phase may also focus on dose response, frequency of dosing, and establishing an optimal dose. Phase 2 studies may enroll patients for several months of study, typically in a randomized trial in which one group of patients receives the study drug of interest and the other, "control" group receives placebo or standard of care. Approximately one-third of phase 2 drugs move on to phase 3.

Phase 3 studies include several hundred to several thousand patients with the target disease and may last several years to establish efficacy and monitor for adverse reactions. Phase 3 studies may make comparisons with placebo or an established treatment to demonstrate improved efficacy or a better risk-benefit ratio. Approximately 25% to 30% of drugs in phase 3 move on to the next stage, which entails submission to the Food and Drug Administration (FDA) to request marketing approval for the new drug.

Phase 4 studies involve several thousand patients and occur after a drug has been approved for the marketplace. They are required for continued monitoring of safety and efficacy on a greater scale and under real-life conditions. In addition, phase 4 studies may explore further targets for which the drug may be used,

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such as new age groups or different dosages or dosing frequencies. In some instances, phase 4 studies may result in a drug having restrictions applied to it or to its being taken completely off the market.

Throughout all phases of clinical drug development, from drug discovery through the lifetime of the marketed drug, safety data are collected and reported for purposes of continuous assessment of risks and benefits. During the 4 phases of clinical drug development, all known safety information is relayed in the informed consent to every potential participant to ensure that they are fully informed of the risks and benefits of study participation. When individuals are enrolled in a study, adverse events (AEs) are collected from the time of enrollment (or other defined time point) to the end time specified in the protocol (conclusion of treatment or withdrawal from the study). All safety data, including those obtained in phase 4, become part of the safety profile of the drug contained in the investigator brochure.

Specific terminology regarding safety has been defined by the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidance: AEs, adverse drug reactions (ADRs), serious AEs (SAEs), expected AEs, unexpected AEs, and suspected unexpected serious adverse reactions (SUSARs). The ICH GCP guidance defines an AE as "…any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product." In contrast, ADRs are defined as "…all noxious and unintended responses to a medicinal product related to any dose." Thus, an ADR is an AE that has a possible causal relationship to the medicinal product. An AE is considered an SAE if it meets any of the following criteria: "…results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital birth anomaly/birth defect." Expected AEs are events that have been previously identified and listed in the investigator brochure compared with an unexpected AE, the "…nature or severity of which is not consistent with the applicable product information." A SUSAR is an SAE the nature and severity of which is not currently part of the investigational drug profile and is judged by either the clinical investigator or the study sponsor as having a reasonable suspected causal relationship to the medicinal product.

These safety terms are extremely important because they form the basis for understanding which types of safety events need to be reported and the process for reporting them to the FDA. The study drug's sponsor has the responsibility to promptly review all safety-related information relevant to the drug, whether obtained from sponsor-related studies or from nonsponsored sources. The sources of safety information include, but are not limited to, animal and in vitro studies, data from clinical or epidemiologic studies, and reports from regulatory authorities in the United States and internationally. The sponsor is then obligated to notify the FDA and all investigators participating in the clinical trial, via an Investigational New Drug safety report, of any potential serious risk. This notification must be completed no later than 15 calendar days after the sponsor's determination that the information qualifies for reporting. See the Table for a listing of what qualifies for FDA reporting. In addition, unexpected fatal or life-threatening suspected ADRs must be reported to the FDA no later than 7 calendar days after the sponsor's receipt of the information.

Drug discovery is a long arduous process, requiring a large investment of financial resources, manpower, and time. The step-by-step framework of drug discovery is highly regulated by the FDA and creates a partnership between the

TABLE. **Qualification for Food and Drug Administration Reporting**

1. Any suspected adverse drug reaction that is both serious and unexpected
    a. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (ie, angioedema or Stevens-Johnson syndrome)
    b. One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the study population (ie, tendon rupture)
    c. An aggregate analysis of a specific event observed in a clinical trial, which may commonly occur in the study population, but which occurs more frequently in the treatment group compared with the control group
2. Findings from other studies, including animal or in vitro studies (not necessarily conducted by the sponsor), that suggest a significant risk in humans associated with exposure to the drug
3. Increased rate of occurrence of serious suspected adverse drug reactions above that listed in the drug's safety profile

FDA and the sponsors to reach the ultimate goal of providing safe and effective drugs for the advancement of public health.

COMMENT: Among the worst moments of my career was the need to tell a mother with AIDS in 1987 that although we now had a first medication (azidothymidine [AZT]) to treat her disease it was not available for her baby, infected at birth. All the drug trials leading to AZT's approval by the FDA had been conducted on adults. Not until 3 years later did a liquid formulation of AZT reach the marketplace when, in 1990, the FDA approved it for use in children. And not until 1997 did congress enact legislation to encourage the inclusion of children in drug trials: under the 1997 law, the patent on a new drug was extended for an additional 6 months if the pharmaceutical company producing it included children in its trials. Despite this incentive, approximately 70% of medications prescribed for children today have been tested only on adults. Likewise, most of the medical and surgical devices used for children have not undergone pediatric trials and do not have FDA approval for their use. Although we have repeatedly proclaimed that children are not little adults, we are forced to use medications and devices without the data appropriate to support their safety and efficacy in our patients. Not to mention that an insurance company may use the lack of FDA approval as grounds for refusing to pay for the off-label use of an expensive medication or device.

– Henry M. Adam, MD
Associate Editor, *In Brief*

Listeria

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AUTHOR DISCLOSURE Dr Lee has disclosed no financial relationships relevant to this article. Dr Krilov has disclosed that he is the site principal investigator for Regeneron Pharmaceuticals Inc and AstraZeneca clinical trials and that he is an advisor at clinical meetings for AstraZeneca. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

If Sir Joseph Lister were alive today, he would be proud that he is remembered as a father of modern surgery and for pioneering antiseptic technique. However, he would be less thrilled that his name is more commonly associated with a household product for halitosis and a bacterium known especially for the outbreaks of foodborne illness it causes: *Listeria monocytogenes.*

Listeria was discovered by Everitt Murray and colleagues in 1926 during a lethal outbreak in perinatal laboratory rabbits. Although the first human case was reported in 1929, neonatal infection was not described until 1936; and despite frequent *Listeria* foodborne outbreaks in the news today, it was not recognized as a cause of outbreaks until 1983.

An intracellular pathogen, *Listeria* relies on mucosal colonization to infect the host through internalization in specific CD8 T cells. The T cells spread *Listeria* to the liver and bloodstream and shield them from macrophages and polymorphonuclear cells. After proliferating intracellularly, *Listeria* escape the phagocytic vacuole and move into the cytoplasm, where they protrude from the plasma membrane as listeriopods, which are then engulfed by neighboring cells. *Listeria, Shigella,* and *Rickettsia* species are the few intracellular bacterial pathogens capable of cell-to-cell dissemination.

Infection with *Listeria* is uncommon, with an incidence of 0.4 to 0.7 cases per 100,000 population in the United States, but causes both serious localized and generalized disease. The annual incidence of listeriosis in the United States for children younger than 12 months ranges from 1 to 12 per 100,000, representing one-third of all cases. The annual incidence is 1% or less in women of childbearing age, except in Hispanic individuals. Clinically, *Listeria* presents in 1 of 4 ways: prepartum infection, neonatal infection, meningitis, and gastroenteritis.

Most pediatric infections occur in the first months of life and present like group B *Streptococcus* (GBS), with either early- or late-onset listeriosis. Early-onset disease presents within 7 days of birth, usually within 24 hours, with pneumonia and sepsis. Infants are infected from mothers who develop *Listeria* chorioamnionitis after eating contaminated food, or through skin and respiratory tract acquisition during birth from mothers with gastrointestinal (GI) or genitourinary colonization. But unlike GBS, human genitourinary carriage is unusual; however, rectal carriage may be as high as 5% in the general population and 30% during outbreaks. *Listeria* is rarely cultured from healthy or premature infants, or cases of intrauterine demise.

Seventy percent of maternal *Listeria* infections result in delivery before 35 weeks' gestation. Mothers often have an influenzalike illness a few days before delivery. At delivery, maternal fever and green or brown amniotic fluid are common. Infected infants may have pustular lesions of the skin and pharynx called *granulomatosis infantisepticum,* as well as granulomatous hepatitis; they may be hypothermic and lethargic. Scattered small salmon-colored truncal papules can

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also develop, as well as microabscesses. Chest radiography may show parenchymal infiltrates suggesting aspiration, or a miliary pattern with multiple discrete lesions. Early-onset sepsis has 40% mortality; survivors typically have no direct sequelae from *Listeria* but may have the complications that can occur in any neonate with pneumonia and sepsis. Early passage of meconium in a premature infant should alert clinicians to consider listeriosis because meconium is rare in infants less than 32 weeks' gestation.

Late-onset listeriosis is less common and typically presents 1 to 8 weeks after delivery with the subtle onset of meningitis in term infants with a benign maternal history. *Listeria* is the third leading cause of bacterial neonatal meningitis, well behind GBS and *Escherichia coli*. Central nervous system infection can also mimic viral encephalitis and, in addition to meningitis, can cause focal brain abscesses. Because of the low concentration of organisms, most cerebrospinal fluid (CSF) Gram-stains are negative for bacteria, but CSF pleocytosis is usual. Mortality is less than 10% with late-onset meningitis. Although hydrocephalus and mental retardation can occur, the outcome may be better than for infants with other bacterial meningitis. Late-onset listeriosis with only colitis, diarrhea, and sepsis has been reported.

Nowadays, we tend to associate *Listeria* with foodborne outbreaks, not neonatal infections. Although gram-negative rods cause most foodborne illnesses, *Listeria* is a gram-positive rod that is a non–spore-forming facultative anaerobe. *Listeria* is almost perfectly adapted to cause foodborne illness in today's world because it tolerates cold, high salt concentrations, and high pH, which allows it to survive in refrigerated and processed foods. *Listeria* can even multiply in the refrigerator. *Listeria* is common in soil, as well as water, sewage, manure, and animal feed, which increases its possibility of entering the food chain through ground vegetables such as cabbage and thus affecting humans. *Listeria* is a common transient colonizer of the GI tract, but, although the prevalence of gut colonization may be as high as 5% in developed countries, listeriosis remains relatively rare, making up less than 1% of bacterial foodborne infections. Invasive disease is far more common in domestic mammals and poultry, especially ruminants such as cattle, sheep, and goats, as well as swine; but despite the large animal reservoir, direct transfer from animals to humans is uncommon. Most listeriosis occurs in newborns and the elderly, but also at increased risk are people with a large GI tract inoculum, patients who are immunocompromised (ie, pregnant women, recipients of cytotoxic chemotherapy, and organ transplant recipients), or those who have chronic medical conditions, such as diabetes, renal failure, cirrhosis, or hemochromatosis.

Common sources of foodborne listeriosis include unpasteurized soft cheeses and other dairy products, undercooked chicken, hot dogs and smoked sausages, smoked fish, and industrially produced, refrigerated, ready-to-eat products ingested without cooking or reheating. Even pasteurization may be insufficient to prevent disease if a high inoculum is present, as occurred in the 1985 California outbreak involving contaminated milk from cows carrying *Listeria*. People at high risk should avoid these foods to protect themselves against listeriosis, as well as salmonellosis and *Campylobacter* infection, which are more common. Despite being far less common than infection with *Salmonella* and *Campylobacter, Listeria* causes more deaths. Mortality is greater than 15% in the estimated 1,600 annual cases of listeriosis in the United States; *Listeria* caused the single deadliest foodborne outbreak in California in 1985 and was the pathogen in 4 of the 5 deadliest global outbreaks.

Typically in otherwise healthy people, *Listeria* causes a self-limited febrile gastroenteritis after a large inoculum from contaminated food, with an attack rate of 50% to 100%. The average incubation period is 24 hours, but it ranges from 6 hours to 10 days. Patients present with fever, watery diarrhea, nausea, vomiting, headache, arthralgias, and myalgias that usually resolve in 2 days or less without sequelae. Bacteremia may complicate the diarrheal disease, especially in the aforementioned high-risk hosts, accounting for the unusually high mortality rate.

Diagnosis relies on isolation in culture because no acceptable serologic tests for *Listeria* exist. Blood cultures are positive in more than one-third of women with infants who have early-onset disease. Stool cultures for *Listeria* are performed on blood agar plates rather than the usual enteric media. Other supportive laboratory tests include the complete blood cell count, which often shows leukocytosis with a shift and a significant monocytosis of up to 20%. Interestingly, monocytosis is not seen in the CSF.

Ampicillin, plus gentamicin for synergy, is the recommended initial treatment for listeriosis, although penicillin, erythromycin, and tetracycline are also recommended because antibiotic resistance is low to these agents. Quinolones, newer macrolides, and imipenem seem to have only moderate activity against *Listeria*, and the organism is resistant to all cephalosporins. Vancomycin and trimethoprim-sulfamethoxazole appear promising, but experience is very limited. Ampicillin is the preferred agent for *Listeria* meningitis and can sterilize the CSF within 36 hours. Approximately 2 weeks of treatment is advised.

COMMENT: So what earned Joseph Lister the honor of having a bacterium named after him? His great contribution to medicine came from the insight that Pasteur's work demonstrating fermentation to result from the action of microorganisms might apply to the pathogenesis of surgical wound infections, until then thought to be the consequence of exposure to foul air known as "miasma." Pasteur had suggested that heat (thus pasteurization) or appropriate chemical contact could kill germs. Lister, rejecting heat as impractical, turned to a chemical, carbolic acid, an agent that had been used to overcome the foul stench of sewage waste. Lister applied carbolic acid directly to open wounds, as well as to surgical instruments, which until his intervention were not routinely washed between patients, and, not surprisingly to us, was able to report remarkable reductions in surgical mortality. Although apparently not a great surgical technician, Lister clearly deserves credit for fathering modern surgery, which could not have developed without his creative thinking.

– Henry M. Adam, MD
Associate Editor, *In Brief*

CME Quiz Correction

An error appeared in the print version of the CME quiz for the December 2017 review "Compartment Syndromes" (Gresh M. *Pediatrics in Review*. 2017;38(12):560-565, DOI: 10.1542/pir.2016-0114). On the fourth quiz question, the beginning of the question stem should read "An orthopedic consultant has evaluated your patient for possible compartment syndrome in the arm and mentions that the child has a delta P of 10 mm Hg." The online version of the quiz is correct, and a correction notice has been posted with the online version of the article. The journal regrets the error.

E-Cigarettes: Effects on the Fetus

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AUTHOR DISCLOSURE Drs Jiang, Zelikoff, and Weitzman and Ms Lee have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The emergence of electronic cigarettes (e-cigarettes) as devices touted to be helpful in the cessation or reduction of smoking has prompted many concerns about the prevalence and consequences of their use during pregnancy. Both pregnant women and health-care providers are poorly informed or misinformed about the potential health risks associated with e-cigarettes, which has profound consequences on clinical conversations about the product. Unfortunately, the scientific literature has not yet caught up with the rise in e-cigarette use. The safety of e-cigarettes to the mother and fetus is largely unknown, with a handful of human studies finding minimal health effects. In large part, concerns about e-cigarettes have been the result of the adverse health effects associated with nicotine during pregnancy, which include low birthweight, abnormal corpus callosum, and alterations in appetite, attention, and cognition. Although the health consequences of e-cigarette use during pregnancy remain poorly understood, it is imperative that health-care providers are well equipped to initiate conversations about e-cigarette use with pregnant women and women of childbearing age to discourage use during pregnancy as an aid to quitting smoking.

E-cigarettes are the most commonly used, newly developed electronic nicotine delivery systems. They are battery-powered vaporizers that heat a liquid solution (typically containing nicotine, glycerol, propylene glycol, flavorings, and other additives) to deliver an aerosol for user inhalation with the intention of imitating conventional cigarettes. Since their introduction to the US market in 2007, e-cigarette use has increased rapidly among youths and adults. E-cigarettes are widely advertised and often are promoted as less harmful alternatives to cigarettes and also as effective smoking cessation tools, which has considerable influence on safety perceptions and subsequent use.

The “harm reduction” and smoking cessation claims emphasized by e-cigarette companies have been shown to be particularly appealing to pregnant smokers, a vulnerable subgroup of smokers with special needs and challenges in smoking cessation. Considering the strong evidence and public health warnings on the adverse effects of prenatal cigarette smoking on maternal and fetal health, pregnant women may be motivated to use e-cigarettes as a safer alternative, if they do not intend to quit. Emerging studies on the prevalence of e-cigarette use during pregnancy have found slightly higher rates of exclusive prenatal e-cigarette use (6.5%) than conventional cigarette use (5.6%).

Perceptions regarding the safety of e-cigarette use during pregnancy vary among different sectors of the general population. More than one-third of pregnant women view e-cigarette use during pregnancy as a safer option than cigarette smoking for both themselves and their fetuses, a perception strongly associated

The Changing Face of Tobacco Use Among United States Youth. Lauterstein D, Hoshino R, Gordon T, Watkins BX, Weitzman M, Zelikoff J. *Curr Drug Abuse Rev*. 2014;7(1):29–43

US Adults’ Perceptions of the Harmful Effects during Pregnancy of Using Electronic Vapor Products Versus Smoking Cigarettes, Styles Survey, 2015. Nguyen KH, Tong VT, Marynak KL, King BA. *Prev Chronic Dis*. 2016;13:E175

The Effects of Electronic Cigarette Emissions on Systemic Cotinine Levels, Weight and Postnatal Lung Growth in Neonatal Mice. McGrath-Morrow SA, Hayashi M, Aherrera A, et al *PLoS One*. 2015;10(2): e0118344 with the high rates of exposure to e-cigarette advertisements in this population. Their belief in the relative safety of e-cigarettes comes despite their lack of knowledge about the ingredients in e-cigarettes and the potential ill effects of these additives. Clinicians, on the other hand, often feel uncertain about e-cigarettes and thus feel ill-equipped to properly advise their patients. Among obstetricians and gynecologists, inconsistent practice on screening for tobacco use and lack of knowledge about the potential risks of e-cigarettes are common, with only 40% of doctors reporting ever asking pregnant women about their use of tobacco. When assessing their perceptions of e-cigarette smoking during pregnancy, 37% of obstetricians and gynecologists reported "don't know," 14% viewed e-cigarettes as harm free, and 29% perceived them as less harmful than tobacco cigarettes. Although no comparable study details what pediatricians know and how they counsel mothers about the harm that e-cigarettes potentially pose to the developing fetus, data do document that pediatricians feel poorly informed about e-cigarettes and seek reliable information on their safety, both before and after birth. The perceived safety and growing popularity of e-cigarettes among the general public, the absence of a consistent stand by health professionals and the public health community, and promotional messages from advertisers all likely contribute to the increasing use of e-cigarettes by pregnant women.

To date, the safety of e-cigarettes to the mother and fetus remains largely unknown. No published study has yet examined the health effects of e-cigarettes on pregnancy or on the outcomes to infants exposed in utero. Laboratory research has concluded that e-cigarettes have lower levels of toxic compounds and carcinogens than cigarettes but contain levels of nicotine that vary from less than to far more than cigarettes. The limited number of studies examining the physiologic and cognitive effects of e-cigarettes on humans have found no or minimal effects on health.

Most of the information we have relating to the health effects of e-cigarettes either stems from animal studies or is extrapolated from evidence on the consequences of nicotine exposure in cigarette smoke. Preliminary data evaluating whether developmental neurotoxicity and later-life behavioral changes are associated with early-life exposure to e-cigarettes seem to be consistent with the extensive literature on exposure to cigarette smoke. Two studies comparing unexposed controls and mice exposed prenatally and postnatally to nicotine-containing e-cigarette aerosols demonstrated that the exposed mice had decreased body weight, higher levels of systemic cotinine, deceased alveolar proliferation, and impairment in postnatal lung growth; they also had higher levels of activity, which could be indicative of behavioral changes from rapid brain growth.

A similar study using non–nicotine-containing and nicotine-containing e-cigarette aerosols found that although e-cigarette aerosols pose a risk to the developing central nervous system, nicotine might not be the driving force for most neurodevelopmental effects, as similar or more extensive effects were seen in offspring exposed to aerosols without nicotine. Despite these findings, nicotine is still widely believed to be the most important neurotoxicant in tobacco smoke in terms of interfering with fetal development. The 2014 Surgeon General's Report authoritatively noted nicotine's lasting adverse consequences on fetal brain development during pregnancy. Nicotine is capable of crossing the placenta and, as early as 7 weeks of gestation, occurs in higher concentrations in fetal fluids than in maternal fluids. The effects of nicotine on prenatal development and postnatal outcomes include sudden infant death syndrome, altered development of the corpus callosum, and alterations in appetite, attention, and cognition.

Animal studies investigating prenatal exposure to nicotine have revealed widespread alterations in gene expression in the brains of offspring, changes that plausibly could influence the structure and function of the corpus callosum, responsible for linking the left and right hemispheres, and resulting in cognitive deficits. Maternal tobacco use during pregnancy is also a major risk factor for increased numbers of nicotine receptors in the fetal/neonatal brain, child tobacco initiation, progression to regular and heavy tobacco use, and nicotine dependence via social, environmental, and genetic mechanisms. The teratogenic effect of maternal smoking during pregnancy may result from the disruption of neural and dopamine systems that modulate sensitivity to nicotine. Research in animals has also suggested that in utero nicotine exposure can lead to a variety of complex behavioral effects, ranging from decreased motivation to enhanced sensitivity to rewards, such as sugary and fatty foods that could increase the likelihood of obesity. In addition, maternal smoking during pregnancy has effects on disruptive behavior disorders, such as attention-deficit/hyperactivity disorder, and has a causal relationship with conduct disorders. Although current literature has attempted to differentiate the risks associated with exposure to nicotine alone versus nicotine exposure in cigarettes, research has not yet established what risks are posed specifically by the nicotine in e-cigarettes. Despite the limited evidence, prudence dictates that pregnant women and women planning to become pregnant who use e-cigarettes should be encouraged to choose ones that are low in nicotine or nicotine free.

The health consequences for mother and child of e-cigarette use during pregnancy and its effectiveness as an aid to smoking cessation remain poorly understood. Given the rapidly increasing use of e-cigarettes, research is urgently needed to define their effects on pregnant women and on the immediate and long-term outcomes for their children, as well as to determine whether e-cigarettes are, in fact, effective aids in smoking cessation.

Also urgently needed are training programs for obstetricians, gynecologists, pediatricians, and other health-care professionals who serve pregnant women or women of childbearing age on the potential risks of perinatal e-cigarette use. Screening of these women should include assessment of e-cigarette use, with advice about the potential adverse consequences of e-cigarette use during pregnancy. Prenatal and pediatric clinicians should emphasize that e-cigarettes deliver varying amounts of nicotine and other potentially toxic constituents and that e-cigarettes are not an approved aid for smoking cessation.

COMMENT: In the face of the uncertainties surrounding the use of e-cigarettes, there are 2 things we can be clear about. The first is that nicotine is highly addictive and, regardless of the questions we may still have about the harms that prenatal exposure poses for the fetus and the child, subjecting a growing brain to an addictive substance that affects several neurotransmitters, including dopamine, has to be akin to playing against loaded dice—not a winning situation. And, second, we can be sure that, similar to the tobacco industry, manufacturers of e-cigarettes and of the liquid solutions they vaporize will aggressively pursue any tactic, whether honest or not, that promotes their products and their profits. Living in a sociopolitical environment that discredits science, we have even more reason to worry that evidence, once gotten, may not be enough to prevail. Our work is cut out for us.

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR MARCH 2018 PEDIATRICS IN REVIEW

Infection Control and Isolation Considerations for the Pediatric Practitioner: 1. B; 2. C; 3. A; 4. D; 5. E.

Pediatric Intracranial Hypertension: 1. B; 2. C; 3. E; 4. D; 5. B.

Acute Abdominal Pain: 1. E; 2. E; 3. D; 4. E; 5. A.

Friend to All Pediatricians

Joseph A. Zenel, MD*
**Editor-in-Chief,* Pediatrics in Review; *Sanford Children's Hospital,
The Sanford School of Medicine, University of South Dakota, Sioux Falls, SD*

If you are a general pediatrician, in some way, Dr Bob Haggerty influenced how you practice medicine. This January Dr Haggerty passed away, leaving quite a legacy, including Chair of Pediatrics at the University of Rochester Medical Center, advocate for ambulatory care and child health, 1984 president of the American Academy of Pediatrics, 1998 recipient of the American Pediatric Society Howland Award, and founding Editor-in-Chief of *Pediatrics in Review.* Bob accomplished even more, but I want to call attention to his love of general pediatrics and for the people who practiced it, not just in academics but in the community; in private practice and free clinics; in rural, urban and suburban settings; in the nation; and in the world. As pediatricians we love and care for children, but in my encounters with him, I observed that deep down, Bob also empathized with all general pediatricians, understood their compassion for children but also their stress of daily practice, the demands on personal time, their coping with exhaustion, and their difficulty with keeping up-to-date on the ever-increasing knowledge of pediatrics. I believe his empathy was the driving force behind his creation of *Pediatrics in Review,* for convincing colleagues in academia and in community practice to collaborate to develop topics for a journal that would "…help improve child health by providing information useful to those professionals who provide health services to children."(1) To protect the purpose of the journal, Dr Haggerty positioned general pediatricians from academia and the private community as part of the editorial board who would serve to verify that what was published was pertinent, readable, evidence-based, concise, and practical. He also enlisted pediatric subspecialists who embraced the concept of the journal and who recognized the importance of general pediatricians as colleagues. Without question Dr Haggerty created camaraderie among all the pediatricians on the board through the years. When he stepped down as Editor-in-Chief, it was again with empathy that Dr Haggerty endorsed Dr Larry Nazarian, a local practicing general pediatrician, as the new Editor-in-Chief of *Pediatrics in Review.* The result of such empathy is a pediatric continuing education journal that is close to 40 years of age and has the largest readership in the world. Throughout his life, Dr Haggerty was an advocate for children, but he was also a mentor and friend to all pediatricians.

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AUTHOR DISCLOSURE Dr Zenel has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

A Privilege to Know Him

Lawrence F. Nazarian, MD*
**Editor Emeritus,* Pediatrics in Review, *Rochester, NY*

We never know how many people we touch, directly or indirectly, by what we do. Dr Robert Haggerty, who passed away in January, improved the lives of countless children in every corner of the world, employing his many skills and interests with tireless dedication. I was fortunate to have him as a mentor, role model, and friend.

In 1964, I was a green intern when Bob arrived in Rochester as chair of the Department of Pediatrics. He soon endeared himself to the house staff with his clear thinking and warm and relaxed manner. Although he was not primarily a practitioner, he impressed us with his clinical acumen. We also discovered that he could predict the future. He defined the "new morbidity," in which pediatricians would be less occupied with treating infectious diseases and busy dealing with developmental, psychological, and social disorders. His predictions came true; when I left practice after 35 years, 40% of my time was occupied with those problems. Through the generosity of Bob and his colleague Stan Friedman and their families, the Haggerty-Friedman Fund supports developmental and behavioral teaching and research at the University of Rochester.

As a result of his seminal work in the area of community pediatrics, Bob was instrumental in establishing a network of neighborhood health centers that brought private-like care to residents of inner city Rochester. His work as President of the W.T. Grant Foundation led to support of a wide range of programs and studies.

I have never met anyone as well-traveled as Bob and his wife and chief supporter, Muriel. In their lake home they had a world map on the wall with a forest of colored pins marking all the places they had been. Bob served as Executive Director of the International Pediatric Association, a position that added myriad pins. Closer to home, he was President of the American Academy of Pediatrics, a position requiring extreme dedication, which took him to foreign lands as well.

Visualize how many children have been touched, through their pediatric clinicians, by his serving as Associate Editor of *The New England Journal of Medicine* and *Pediatrics,* as well as through the practitioner's best friend, *Pediatrics in Review,* which he conceived, founded, and edited.

To list all of Bob Haggerty's accomplishments and awards would take many pages. I see him now, comparing notes on our raspberry patches and filling me in on his grandchildren's activities, all the while reaching out to all children in so many ways. A life well lived!

AUTHOR DISCLOSURE Dr Nazarian has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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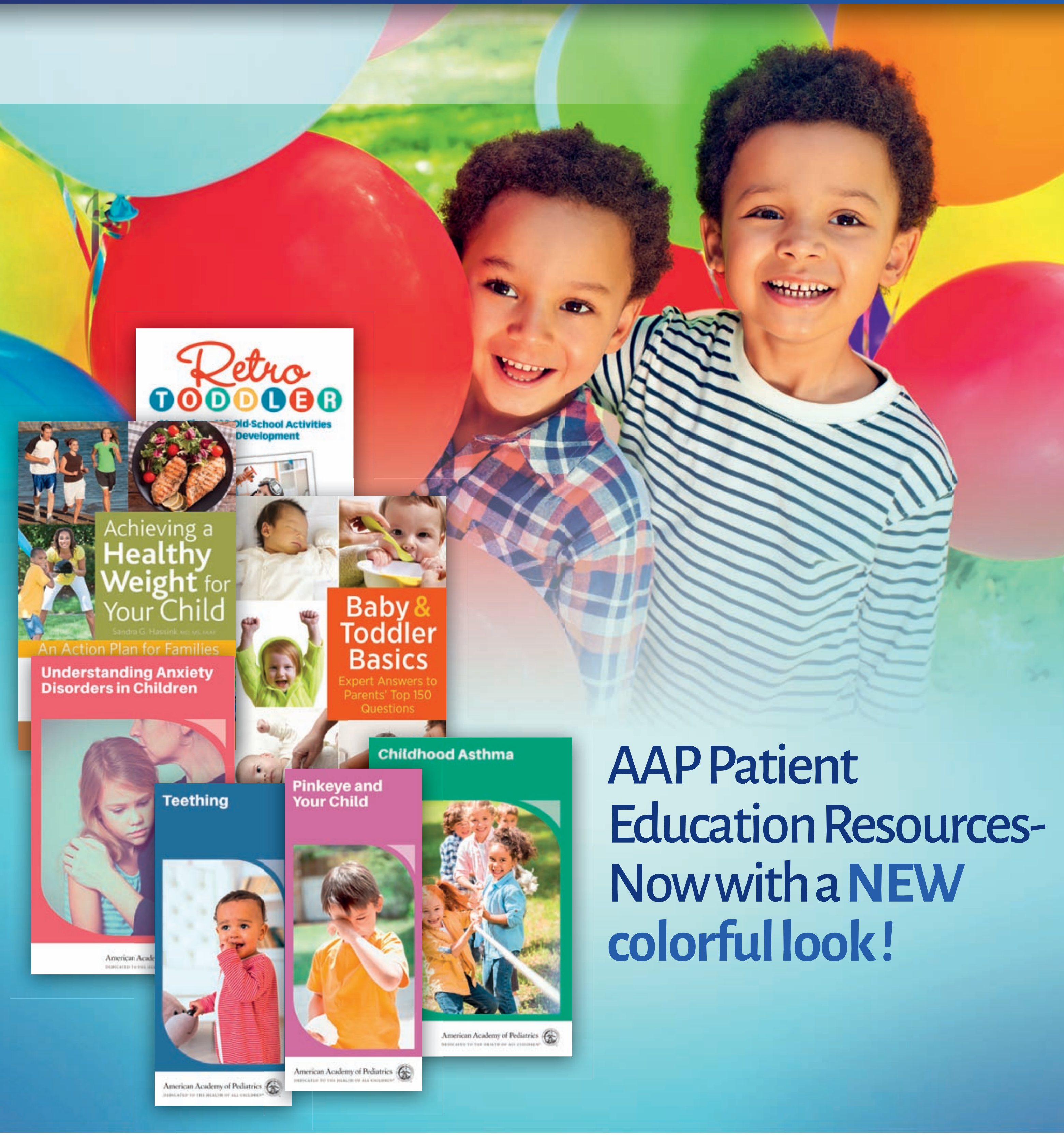
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Visual Diagnosis

Recurrent Seizures and Concomitant Skin Changes in a 16-year-old Boy

Neha Gupta, MD,* Saurabh Talathi, MD, MPH,* Yenimar Ventura, MD,*
Sergey Prokhorov, MD*

**Department of Pediatrics, Lincoln Medical Center, Bronx, NY*

PRESENTATION

A 16-year-old Hispanic boy with a history of intermittent asthma presents to the emergency department (ED) with recurrent unprovoked seizures. The first episode was 2 weeks before this visit and was characterized by generalized tonic-clonic seizures (GCTSs), with a postictal phase of 10 minutes. He was seen in the ED during that episode, with normal findings on examination and evaluation, including a complete blood cell count, chemistry, liver function tests, urine toxicology, and a computed tomographic (CT) scan. During the current visit, he presents with a history of 2 episodes of unprovoked GTCSs 4 hours apart. The first episode lasted 5 minutes, followed by a postictal phase of 5 minutes. In the ED, he has normal physical examination findings and is discharged on oral oxcarbazepine with a diagnosis of idiopathic epilepsy. Before starting the prescribed medication, he develops another episode of GCTSs, approximately 7 to 8 minutes, with no postictal phase. Each of these episodes were preceded by coughing spells lasting 10 to 20 minutes. He has no history of fever, head trauma, recent travel, drug intake, medication use, or sick contacts.

In the ED, his vital signs are normal except for intermittent bradycardia (heart rate, 60 beats/min). Physical examination findings are normal except for bite marks on the right side of the tongue. Results of a complete blood cell count, chemistry, liver function tests, and urinalysis are within normal limits. Urine toxicology results are negative. Findings from electrocardiography (ECG), electroencephalography (EEG), and brain magnetic resonance imaging (MRI) are normal. The patient is started on divalproex. Primary generalized epilepsy is suspected by the ED physician for undocumented reasons, and the patient is discharged on divalproex.

Four months after the ED visit, the patient presents to the neurology clinic for a follow-up visit. He is found to have mild left-sided linear facial atrophy, with mild sclerosis and hyperpigmentation just below the left eye, and asymmetry of the left angle of the mouth (Fig 1). The patient is referred to the dermatology department for suspected scleroderma. An autoimmune and viral evaluation is performed, including antinuclear antibody, anti-Scl antibody, varicella-zoster virus antibody, Lyme antibody, herpes simplex virus, Epstein-Barr virus polymerase chain reactions, and human immunodeficiency virus enzyme-linked immunosorbent assay. A facial radiograph is normal. Biopsy of the skin lesion confirms the diagnosis.

DIAGNOSIS

Based on the clinical picture and the hemifacial atrophy, the patient is diagnosed as having Parry-Romberg syndrome (PRS) by the dermatologist. The diagnosis is

AUTHOR DISCLOSURE Drs Gupta, Talathi, Ventura, and Prokhorov have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

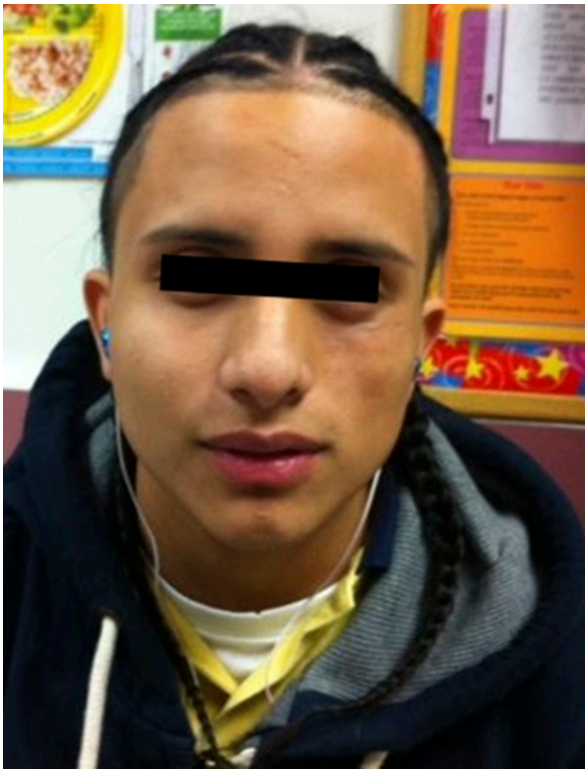

Figure 1. Mild left-sided facial atrophy. There is a sclerotic lesion just below the left eye associated with mild hyperpigmentation. The angles of the mouth also are asymmetrical, with the left side drooping slightly compared with the right.

confirmed by a biopsy of the skin showing sparse perivascular dermatitis with decreased elastic tissue.

DISCUSSION

Parry-Romberg syndrome is a rare idiopathic disease characterized by progressive hemifacial atrophy affecting the skin, subcutaneous tissue, muscles, and sometimes skeletal structures. The progression of the disease varies from 2 to 20 years before stabilization. (1) It is more common in females, but males can also be affected, as in the present case. (1)(2)(3)(4) Generally, PRS presents at the end of the first decade of life; however, there is a lack of early recognition. (1)(2)(3)(4) Literature review shows a delay in diagnosis of PRS by approximately 1.5 to 4 years. (2)(3)

Parry-Romberg syndrome is associated with systemic manifestations, with neurologic manifestations being one of the most common, affecting 13% to 34% of patients. (1)(4) The most common neurologic manifestation is seizures, with a frequency of 8% to 21%. (1)(2)(3)(4)(5) Migraines, facial pain, hemiplegia, aneurysm, brain atrophy, and limb atrophy have also been reported in patients with PRS. (1)(2)(6)(7)(8)(9)(10)(11) Other system involvements may include ophthalmologic, (1)(2)(3)(10)(12)(13)(14)(15)(16)(17) cardiac, (18) rheumatologic, (2)(19) and maxillofacial and dental abnormalities. (1)(7)(20)(21) Although the mechanism of these associated abnormalities is unclear, a multisystem origin is hypothesized. (22) An early case report by Lonchampt et al (23) reported abnormal electromyographic, blink reflex, and trigeminal evoked potential studies in their patient with PRS. This suggests that there may be autoimmune-mediated hyperactivity of brain stem sympathetic centers involving the noradrenergic system. (23) It has also been hypothesized that PRS is a disorder of neural crest migration, thus explaining the constellation of symptoms in different organ systems derived from neural crest cells. (24)

A seminal paper by Fry and colleagues (25) found that a small sample of patients with PRS developed neurologic dysfunction with cerebral lesions on MRI, leading to the concept that PRS is a regional immune-mediated disorder affecting multiple tissue lines in the area of disease. Indeed, the most common brain MRI finding in PRS is white matter high signal intensity in T2, usually ipsilateral to the skin lesions, that can be detected years after the onset of skin lesions. (1)(3)(5) Because results of imaging studies do not always correlate with disease severity, it has been recommended to perform brain MRI or CT scan studies after PRS is diagnosed even in patients free of neurologic symptoms. (26) Other imaging findings are hyperintensities in T1 in the frontal lobe and corpus callosum and gliomatosis. (3)(5) Blaszczyk et al (5) found decreased cerebral blood flow in ~70% patients with PRS when measured using single-photon emission CT. However, reduced blood flow is likely secondary to PRS-associated atrophy rather than being a cause of PRS symptoms.

Findings on EEG in PRS can be varied, including temporal or frontotemporal discharges, frontal slowing, generalized abnormalities, depression, or ipsilateral multifocal sharp waves. (1)(2)(5) Interestingly, our patient also had coughing spells, which may have been epileptic auras signifying a temporal epileptic focus, the suspicion of which was further supported by the finding of temporal discharges on our patient's EEG (Fig 2). Skin biopsy in PRS can include epidermal atrophy, dermal sclerosis, entrapment of eccrine coils, inflammatory infiltrate, perivascular lymphocytic infiltrate, atrophy, and slight fibrosis. (1)(5)

There are 2 conditions described in association with PRS: linear scleroderma en coup de sabre (LSCS) and Rasmussen encephalitis. The differentiation between PRS and LSCS is difficult to the extent that some describe these conditions as part of the same spectrum. (2)(6)(7)(8)

A form of localized linear scleroderma of the face, LSCS is characterized by a lesion of the frontoparietal scalp area. (1)(2) Studies have found that approximately half of the patients with PRS also had en coup de sabre lesions. Moreover, any

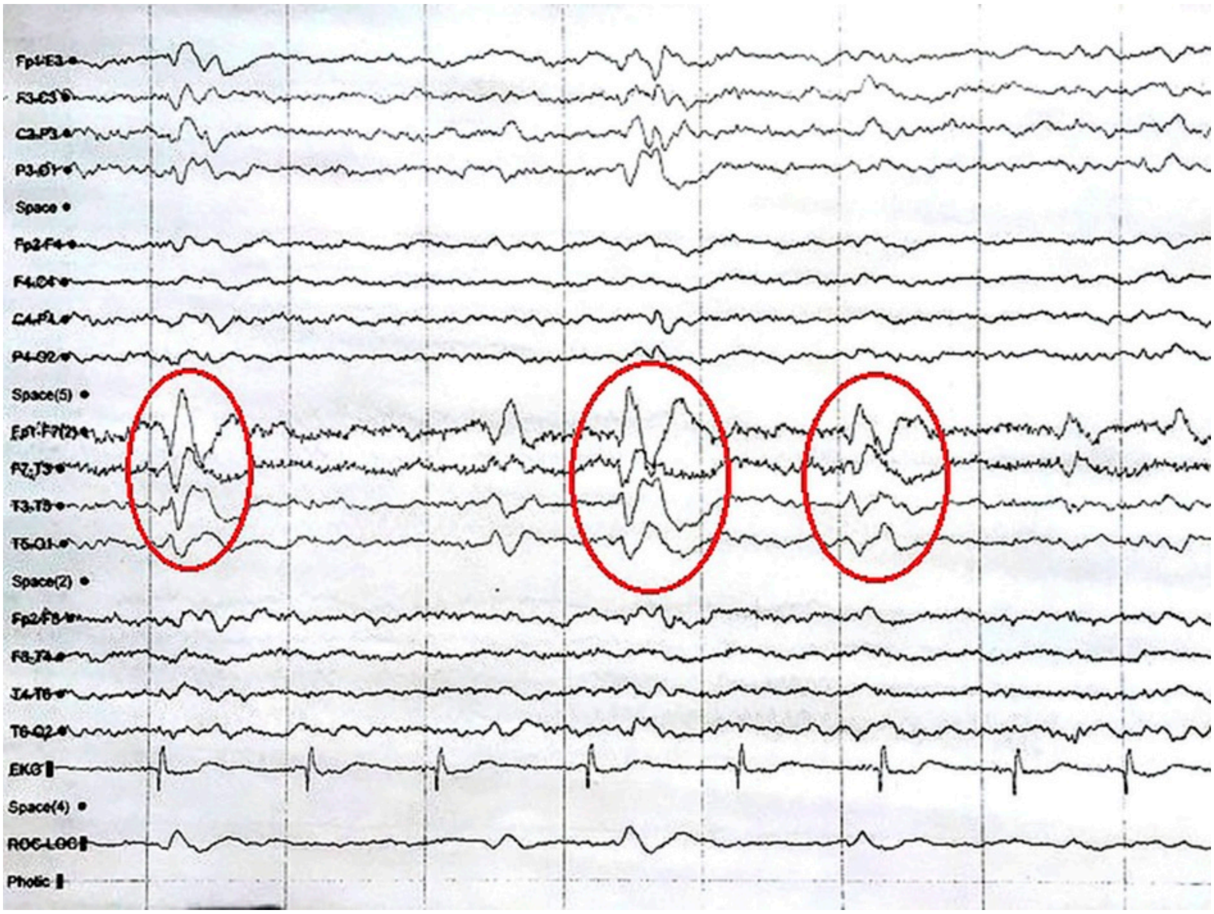

Figure 2. Interictal electroencephalogram demonstrating spikes in the left temporal lobe. The location of these spikes can be considered as the site of the patient's main neurologic dysfunction, the coughing spells being an aura originating from the temporal lobe.

condition mimicking a scleroderma can be a differential diagnosis of PRS, including lichen sclerosis, lupus panniculitis, and other autoimmune conditions.

Management of patients with PRS is challenging because there are no agreed on guidelines. Patients with seizures need symptomatic treatment with antiepileptics. Topical corticosteroids, hydroxychloroquine, oral antibiotics, penicillamine, prednisone, methotrexate, vitamin E, and pulse laser have been used with varying degrees of success for skin findings. (1)(2) Due to the rarity of the condition, none of these treatment options have been tested in a randomized controlled trial. Further investigations are needed regarding the efficacy of these treatment options.

The prognosis of PRS is highly variable. There is inconsistency in the pattern of atrophy, and thus it is difficult to determine which patients may develop secondary symptoms. (27) Controlling the disease progression is the primary focus. In some patients, atrophy stops before affecting the entire face, whereas in others, it might progress to affect the face more globally. In mild cases, there is no disability, except for cosmetic effects. (28) However, in some cases, complications might lead to eventual death of a patient. Although most patients do recover, the recovery period is unpredictable and individualized. (28)

PATIENT COURSE

After the diagnosis of PRS, immunosuppressive therapy with methotrexate was initiated, with folic acid supplementation. His evaluation for Sjögren syndrome, varicella-zoster virus antibody, Lyme antibody, herpes simplex virus, Epstein-Barr virus polymerase chain reactions, and human immunodeficiency virus enzyme-linked immunosorbent assay was reported negative. He developed another episode of GCTSs 1 month later due to noncompliance with antiseizure medication. The valproic acid level in the blood was low, and the dose was readjusted. Results of a repeated brain MRI and magnetic resonance angiography were normal. The third EEG revealed epileptiform spikes in the left temporal lobe (Fig 2). Video-EEG monitoring also revealed epileptic activity in the left temporal-occipital region. Carbamazepine was substituted for divalproex sodium. The patient had a drug eruption with carbamazepine and was switched to levetiracetam, on which he stayed symptom free. As of his last visit, the patient's seizures are under control with the current medications, and his hemifacial atrophy has improved but is not completely resolved.

Summary

- Seizure disorders may indicate an underlying syndromic association. A detailed physical examination and a complete evaluation, with close follow-up, may expedite diagnosis of such conditions and thus prevent potentially irreversible outcomes.
- A high index of suspicion should be maintained while evaluating a patient with seizure disorder, with history and physical examination being an imperative part of the evaluation.
- This case illustrates that, albeit rare, Parry-Romberg syndrome (PRS) should be included in the differential diagnosis of patients with seizures and concomitant skin changes in the form of scleroderma.
- Owing to highly variable findings and lack of predictability in determining patients with PRS who may develop secondary complications, it becomes difficult to diagnose and prognosticate. As such, early referral to a neurologist or dermatologist, in conjunction with magnetic resonance imaging, should be considered if indicated.

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Connective Tissue Nevus and Osteopoikilosis

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PRESENTATION

A 7-year-old boy presents to pediatric consultation with a 5-year history of progressively enlarging and multiplying asymptomatic skin lesions distributed over the right thigh, back, and abdomen. He has no other complaints or relevant medical history. Histopathologic analysis of a punch biopsy from the right thigh performed when the child was 3 years old was suggestive of a nevus lipomatodes superficialis.

The maternal family history is notable for osteopoikilosis in members of the 3 previous generations, including his mother (Fig 1) and an aunt who has been evaluated for metastatic bone disease because of radiographic findings. There is no family history of similar skin lesions.

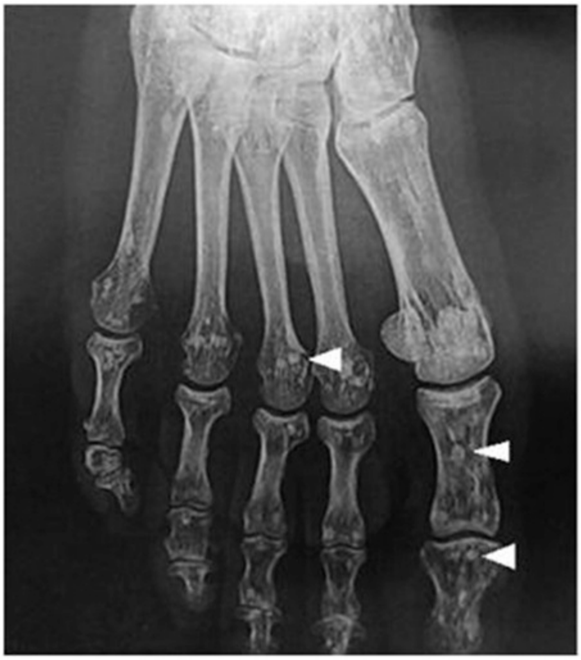

Figure 1. Right foot radiograph of the mother showing multiple small round hyperdense foci of osteopoikilosis (arrowheads).

AUTHOR DISCLOSURE Drs Pereira, Leite, Ferreira, and Duarte and Profs Haneke and Correia have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Physical examination reveals asymmetrically distributed papules and nodules, 10 to 18 mm in diameter, coalescing into plaques in the anterior surface of his right thigh, sacral region, and left lower abdomen. They have irregular contours, a yellow hue, a smooth surface, and a firm rubbery consistency (Fig 2).

Histopathologic analysis of a punch biopsy sample from the right thigh at this age is again diagnosed as a nevus lipomatodes superficialis. However, further review of the same biopsy yields the features of a typical cutaneous tissue nevus (CTN) with an increase of elastic fibers and irregular arrangement of the collagen tissue fibers. The overlying epidermis is normal, and there is no inflammatory infiltrate and no increase in the number of histiocytes. Elastic stain shows a slight increase in the number of elastic fibers, some with a frayed appearance (Fig 3).

Skeletal radiographs of the hands, wrists, knees, ankles, feet, and pelvis reveal small round radiopaque foci suggestive of osteopoikilosis in the second metacarpal and third middle phalanx of the left hand (Fig 4), right talus, and cuboid bones, as well as larger oval radiopacities in the distal metaphysis of the right femur and the tibia and fibula bilaterally (Fig 5).

DIAGNOSIS

The association of CTN and osteopoikilosis allowed the clinical diagnosis of Buschke-Ollendorff syndrome (BOS). Genotyping confirmed the diagnosis, revealing a heterozygous known pathogenic mutation in *LEMD3* (c.1323C»A (p.Tyr441X)). (1)

DISCUSSION

The BOS is a rare connective tissue disorder inherited in an autosomal dominant pattern (2)(3)(4)(5) and characterized by the association of CTN and osteopoikilosis. (2)(4)(6)

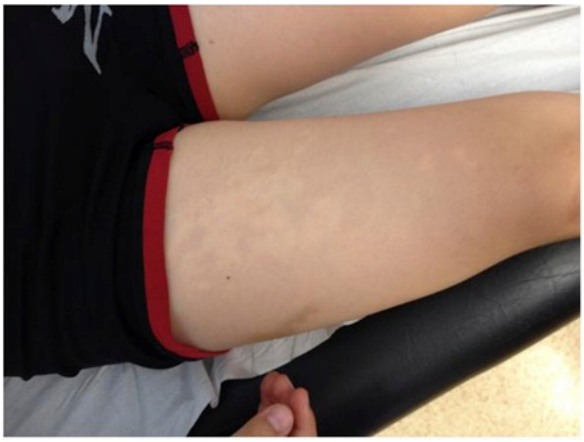

Figure 2. Right thigh anterior surface papular skin lesions in the child coalescing into plaques, with irregular contours, a yellow tone, a smooth surface, and a firm rubbery consistency.

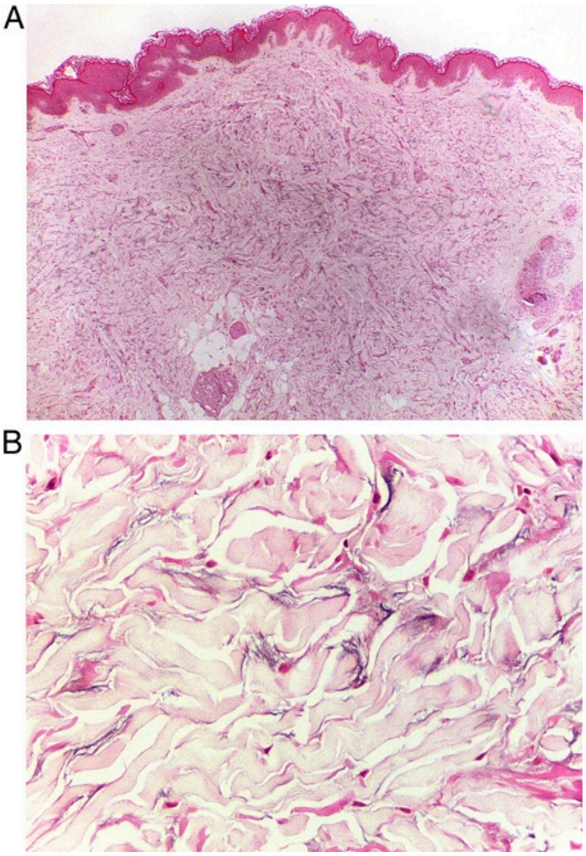

Figure 3. A. Histologic picture of the skin biopsy sample from the right thigh performed at age 7 years showing a slightly myxoid dermatofibroma with an increase in elastic fibers, irregular arrangement of the connective tissue fibers, and normal overlying epidermis, suggesting the diagnosis of a cutaneous tissue nevus (elastic stain, magnification ×40). B. Higher magnification (×400) of the same biopsy specimen shows an increase in the number of elastic fibers with a frayed appearance.

It was first described in 1928 by Buschke and Ollendorff, and since then, approximately 100 cases have been reported. (7) It has an estimated incidence of 1 in 20,000 (4)(7)(8) and usually presents in the first 2 decades of life, (7) with a male to female ratio of 1:1. (9) It has a variable phenotypic expression, (2)(4)(5)(10) with bone and skin lesions occasionally occurring independently in different family members, (2)(7) as in the present case.

Cutaneous tissue nevi are dermal hamartomas characterized by an imbalance in the amount and distribution of the extracellular dermal matrix components elastin, collagen, and/or proteoglycans (11). They can be located anywhere in the body surface but in BOS they occur more frequently on the trunk and extremities. (3)(8) Typically, they are asymptomatic and, therefore, frequently overlooked. (11) Physical examination usually reveals flesh-colored or yellow nodules or papules with firm and rubbery consistency that may coalesce into plaques. (8)(11) In BOS, they usually represent 1 of 2 patterns (4)(5): the most common and presented herein is characterized by

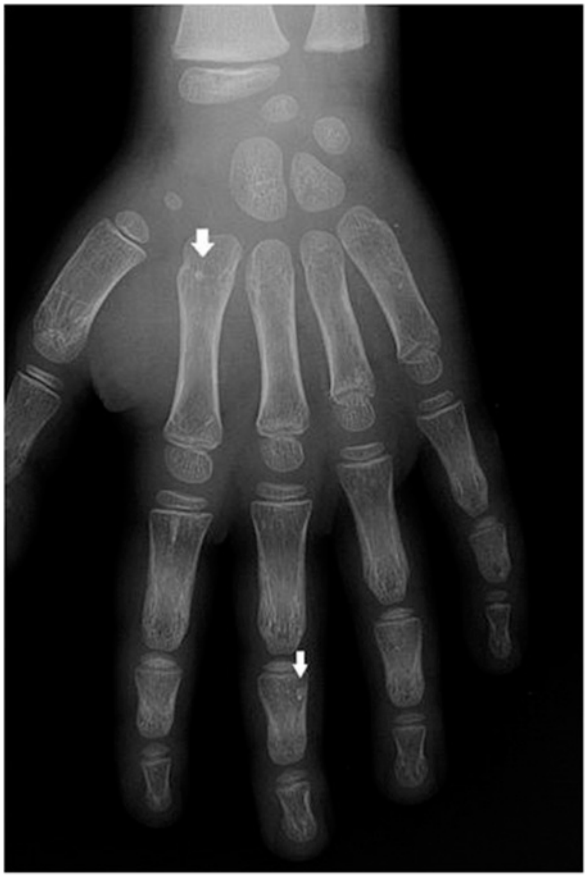

Figure 4. Small round osteopoikilotic foci in the second metacarpal and third middle phalanx of the left hand (arrows).

skin nodules or papules of a yellow hue that coalesce into localized asymmetrically distributed plaques (4)(5)(11)(12); the other is characterized by smaller, diffusely and symmetrically distributed, uniform, flesh-colored or yellow papules. (4)(5)(12) They usually present at birth or in early childhood (3) and can increase in size and number over time. (3)(11)

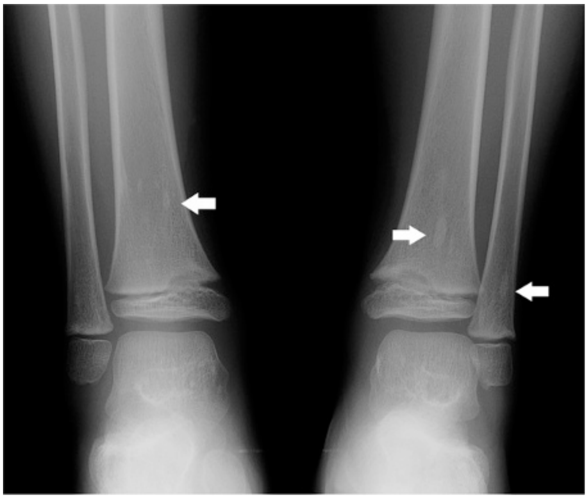

Figure 5. Large oval foci of osteopoikilosis in the child's distal metaphysis of the right and left tibia and left fibula (arrows).

The differential diagnosis of skin lesions clinically similar to CTN includes smooth muscle hamartoma, fibromatosis, granuloma annulare, anetoderma, lichen amyloidosis, morphea, scars, and epidermal and sebaceous nevi. (11) Furthermore, CTN can be sporadic (as in eruptive collagenoma and isolated elastoma/collagenoma) or familial (as in familial collagenoma/elastoma) and can also be part of other clinical syndromes, such as tuberous sclerosis, Proteus syndrome, and multiple endocrine neoplasia type 1. (11) Along with the personal and family history and physical examination, the histopathologic diagnosis of CTN and identification of its predominant extracellular matrix component can aid in this differential diagnosis. (11) In BOS, CTNs most often reveal increased elastin fibers in normal collagen bundles (juvenile elastoma), although proliferation and hyperplasia of collagen fibers can predominate (dermatofibrosis lenticularis disseminata) or be concomitant. (4)(5)(7)(11) To avoid false-negative results, the biopsy specimen should have a 5- to 6-mm depth from the epidermal surface and should include adjacent normal-appearing skin for comparison. (11) Even so, as in this case, the diagnosis of CTN may still be difficult and require multiple skin biopsies or consultation with expert dermatopathologists.

Osteopoikilosis is a benign skeletal dysplasia (4)(9) characterized by a periarticular distribution of osteosclerotic foci in the appendicular skeleton. (13). It has an estimated prevalence of 1 in 50,000 (13)(14) and appears gradually and more prominently during puberty, (3)(5)(7)(8) persisting throughout life, (8)(9) which may explain the radiologic disparity in the number of foci between the mother and child in the case presented. It is usually asymptomatic (3)(4)(5)(8)(10)(13) and does not increase the risk of fracture, (4)(5) although skeletal pain and articular edema are described in 15% to 25% of patients. (9) Skeletal radiographs are characterized by hyperdense foci in the phalanges; carpal, metacarpal, and tarsal bones; epiphysis and metaphysis of the long bones; and pelvis (3)(4)(7)(9)(11)(14); therefore, a limited rather than an entire skeletal survey will generally yield accurate results while minimizing radiation exposure. (11) Osteopoikilotic foci are usually bilateral and symmetrical, with round or oval contours and a diameter of 1 to 10 mm. (3)(4)(8)(11) Although larger solitary lesions have been described in the long bone metaphysis, (7) these are usually incidental findings. (7)(13)(14) Osteopoikilosis may be the only manifestation of BOS, (7) leading to an erroneous suspicion of osteoblastic metastasis, (4)(5)(7)(9)(10)(12) with further costly, unnecessary, and frequently stressful investigations, (4)(7)(9)(11)(12), possibly the case in the aunt of our patient.

LEMD3 is the only gene known to be associated with BOS. (4)(6) Located on chromosome 12q14, (2)(9) it encodes an inner nuclear membrane protein (3) that acts in the transforming growth factor β and bone morphogenetic protein signaling pathways, inhibiting connective tissue morphogenesis. (4)(6) Its inactivation induces these signaling pathways, (6) ultimately stimulating the production of elastin, type 1 collagen, and fibronectin. (9) This mutation is described in cases of osteopoikilosis, CTN, and melorheostosis, suggesting a common pathogenic pathway, (15) although its absence in some affected individuals and families (5)(15) raises the possibility of genetic heterogenicity, (2)(5)(15) which is yet to be confirmed. (2)

There are reported cases of BOS associated with hypertrophic scar formation after skin trauma, (2) otosclerosis, (5)(7)(11) congenital spinal stenosis, (5)(7)(11) craniosynostosis, (7)(8)(11) nail patella syndrome, (7)(11) short stature, (5)(11) muscular contracture, (5)(11) supranumerary ribs and vertebra, (11) articular hypermotility, (11) diabetes mellitus, (5)(11) neuropathy, (11) ocular abnormalities, (5)(11) cryptorchism, (5)(11) and peptic ulcer disease. (5)(8) However, these associations are rare and probably coincidental.

The BOS is a benign genodermatosis (5)(12) and does not require specific treatment (4)(5)(9)(12) because most cases are asymptomatic, with no long-term sequelae (4)(5)(11) or significant cosmetic burden. (4)

After 3 years of follow-up there is an increase in the number of skin lesions and intermittent leg pain that does not interfere with daily activities.

Summary

- Buschke-Ollendorff syndrome (BOS) is a benign entity characterized by the association of cutaneous tissue nevus and osteopoikilosis.
- It has a variable phenotypic expression that may delay diagnosis, and osteopoikilosis alone may be misdiagnosed as bone metastases if this condition is not considered.
- A high index of suspicion and a multidisciplinary approach are important for a correct and timely diagnosis, avoiding costly, unnecessary, and frequently stressful investigations. (4)(7)(9)(11)(12) Detailed personal and family histories and physical examination are crucial to the initial suspicion. (11) Skin lesion biopsy may help to confirm and categorize cutaneous tissue nevus, and limited radiographs can detect osteopoikilosis. (11)
- Although the familial association of typical skin and skeletal changes allows clinical diagnosis of BOS, (4)(7)(12) identification of the *LEMD3* mutation is useful when there is phenotypic variability within a family or between sporadic cases.

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Suggested Readings

Korekawa A, Nakano H, Toyomaki Y, et al. Buschke-Ollendorff syndrome associated with hypertrophic scar formation: a possible role for *LEMD3* mutation. *Br J Dermatol.* 2012;166(4):900–903

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- Philip Fischer, MD, disclosed he has received honoraria from Relias Learning (AHC Media).
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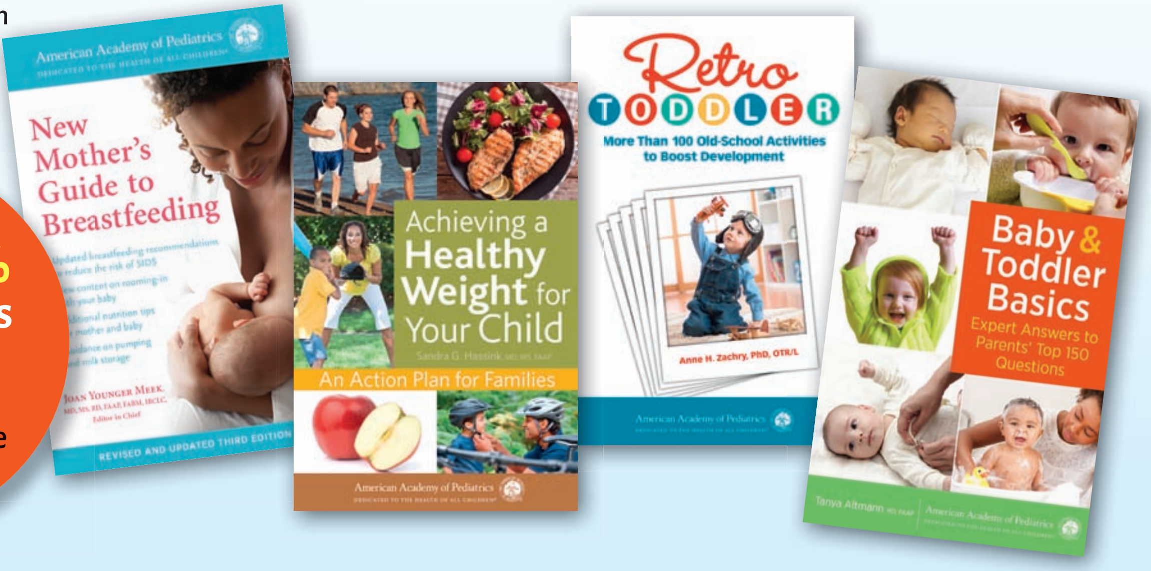
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BEXSERO®
Meningococcal Group B Vaccine

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4 COMPONENTS

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2 DOSES

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AS FAST AS 1 MONTH

The dosing schedule for BEXSERO allows your patients to complete the series within the span of 1 typical summer break.[1]

Talk with your adolescent patients about vaccinating against MenB
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Indication for BEXSERO

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

- BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO
- Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals
- Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope
- The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%)
- Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains
- Vaccination with BEXSERO may not result in protection in all vaccine recipients

Please see accompanying brief summary of full Prescribing Information for BEXSERO.

References: 1. Prescribing Information for BEXSERO. **2.** Prescribing Information for TRUMENBA.

BEXSERO is a registered trademark of the GSK group of companies.

BRIEF SUMMARY

BEXSERO® (Meningococcal Group B Vaccine)
Suspension for intramuscular injection

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO® is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. *[see Description (11) of full prescribing information]*

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of vaccine effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1) of full prescribing information]*.

5.5 Altered Immunocompetence

Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In four clinical trials, 3058 individuals 10 through 25 years of age received at least one dose of BEXSERO, 1436 participants received only BEXSERO, 2089 received only placebo or a control vaccine, and 1622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in US and Poland, 120 participants 10 through 25 years of age received at least one dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by Menveo [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM$_{197}$ Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49% and 60% were White; 34% were Hispanic, 4% were Black,<1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) 11 through 17 years of age received at least one dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (UK), 974 university students 18 through 24 years of age received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1 dose of Menveo followed by 1 dose of placebo containing aluminum hydroxide (N=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (N=947). Across groups, median age was 20 years, males comprised 46%, and 88% were White, 5% were Asian, 2% were Black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were White, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, US/Poland, Canada/Australia, and in a subset of participants in the UK study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the US/Poland study, reports of unsolicited adverse events were collected up to one month after the second vaccination.

Reports of all serious adverse events, medically attended adverse events and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), UK (12 months), US/Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants 10 through 25 years of age following each dose of BEXSERO administered 2 months apart or control in the US/Polish study[1] are presented in Table 1.

Table 1: Percentage of US and Polish Participants 10 through 25 Years of Age Reporting Solicited Local and Systemic Adverse Reactions within 7 Days after BEXSERO or Control, by Dose

Solicited Reaction[a]		Dose 1		Dose 2[b]	
		BEXSERO	Placebo (Saline)	BEXSERO	Menveo
		N=110-114	N= 94-96	N=107-109	N=90-92
Local Adverse Reactions					
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	> 50-100 mm	1	1	2	4
	> 100 mm	0	0	0	2
Systemic Adverse Reactions					
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

Clinicaltrials.gov Identifier NCT01272180.

[a] Erythema, and induration: Any (≥ 1 mm). Pain and systemic reactions: mild (transient with no limitation in normal daily activity); moderate (some limitation in normal daily activity); severe (unable to perform normal daily activity)

[b] Administered 2 months after Dose 1

Solicited adverse reaction rates were similar among participants 11 through 24 years of age who received BEXSERO in the other three clinical studies,[2,3,4] except for severe myalgia which was reported by 3-7% of subjects. Severe pain was reported by 8% of university students in the UK[3].

(continued on next page)

Non-serious Adverse Events

In the 3 controlled studies[1,2,3] (BEXSERO N=2221, control N=2204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) BEXSERO and 197 (9%) control recipients. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in BEXSERO recipients than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants 10 through 25 years of age who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO N=2716, Control N=2078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) BEXSERO recipients and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at two universities in the US, BEXSERO was administered as a 2 dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals 16 through 65 years of age who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one event considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

Adverse event reports received for BEXSERO marketed outside the US are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency, or to establish a causal relationship to vaccination. This list includes serious events or events which have suspected causal association to BEXSERO.

General disorders and administration site conditions:	Blisters at or around the injection site.
Immune System Disorders:	Allergic reactions (including anaphylactic reactions), rash, eye swelling.
Nervous System Disorders:	Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility in females or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Pregnancy Registry for BEXSERO

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to BEXSERO during pregnancy. Women who receive BEXSERO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years of age.

15 REFERENCES

1. NCT01272180 (V102_03)
2. NCT00661713 (V72P10)
3. NCT01214850 (V72_29)
4. NCT01423084 (V72_41)
5. Wang X, et al. *Vaccine.* 2011; 29:4739-4744.
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17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling.*

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Vitamin Excess and Deficiency

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*Section of Nutrition, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO

Education Gap

Vitamins are organic compounds that humans cannot synthesize but need in small amounts to sustain life.

Pediatricians' knowledge about vitamins is challenged daily. Pediatricians are faced not only with parents requesting supplements but also with parents refusing them when they are clinically indicated.

In addition, pediatricians need to be familiar with the effect of maternal health and diet on human milk to counsel their patients on how to prevent potentially devastating health consequences for the breastfed infant.

Tables 1 and 2 provide the reader with a quick reference to who is at risk and when to consider a vitamin or mineral deficiency (minerals will be covered in the second part of this review). Table 3 summarizes the pharmaceutical and supplemental sources of vitamin D and Table 4 provides a quick reference for diagnostic tests and treatment doses for vitamin deficiencies.

Objectives

After completing this article, readers should be able to:

1. Discuss the risk factors for developing selected vitamin deficiencies.
2. Identify the role of natural foods, fortified foods, and supplements in meeting the Dietary Reference Intakes of various vitamins.
3. Discuss the biological functions of various vitamins and their role in disease prevention.
4. Describe the clinical symptoms of various vitamin deficiencies and the role of laboratory data in making the diagnosis.
5. Explain treatment and prevention strategies for various vitamin deficiencies.

Abstract

The published literature supports the high prevalence of supplement use in children and adolescents in the United States. Pediatricians today are faced with questions from parents and patients about the benefits, safety, efficacy, and correct dose of vitamins and minerals. In this article, we review 7 vitamins with the most clinical relevance as judged by abundance in food, risks and symptoms of deficiency, and potential for

AUTHOR DISCLOSURE Drs Diab and Krebs have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
CT	computed tomography
DRIs	Dietary Reference Intakes
FDA	Food and Drug Administration
ICH	intracranial hemorrhage
IF	intrinsic factor
IM	intramuscular
IOM	Institute of Medicine
MMA	methylmalonic acid
NASH	nonalcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NTD	neural tube defect
PIVKA	proteins induced by vitamin K absence
PTH	parathyroid hormone
RAE	retinol activity equivalent
RDA	Recommended Dietary Allowance
UL	Tolerable Upper Intake Level
VKDB	vitamin K deficiency bleeding
1,25(OH)2D	1,25 dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D

toxicity. Specifically, we focus on possible clinical scenarios that can be indicative of nutritional deficiency. We synthesize and summarize guidelines from nutrition experts, various medical societies, the World Health Organization, and the American Academy of Pediatrics.

PREVALENCE OF SUPPLEMENT USE IN THE UNITED STATES

The published literature supports the high prevalence of supplement use in children and adolescents in the United States. According to the National Health and Nutrition Examination Survey (NHANES), 34% of US children and adolescents used supplements in the past month, and almost half of those took a supplement daily. Supplement use was high in underweight patients. (1) Supplement users were more likely to be Asian, white, or non-Hispanic; to belong to families with higher income and education; to be in good or excellent health; and to have access to health care. (2)

THE DIETARY REFERENCE INTAKES

According to the Institute of Medicine (IOM), the Dietary Reference Intakes (DRIs) include 4 nutrient-based reference values that are used to assess and plan the diet of healthy people:

- Estimated Average Requirement: the average daily nutrient intake level that is sufficient to meet the requirements of half of the healthy population of a particular age and sex
- Recommended Dietary Allowance (RDA): the average daily nutrient intake level that is sufficient to meet the requirements of nearly all (97%–98%) of the healthy individual of a particular age and sex
- Adequate intake: the recommended average daily intake level based on estimated intake of apparently healthy people; adequate intake is used when RDA cannot be determined
- Tolerable Upper Intake Level (UL): the highest average daily nutrient intake level that is unlikely to pose a risk of adverse effects to almost the whole general population (3)

VITAMIN A (RETINOL)

Introduction

Until the 1980s, the focus on vitamin A deficiency was limited to its ocular manifestations as the leading cause of blindness in developing countries. However, in the past 3 decades, international studies indicate that subclinical vitamin A deficiency has broader consequences regarding childhood morbidity and mortality in the developing world. Vitamin A deficiency accounts for 1.7% of all deaths in children younger than 5 years in developing countries. (4)

Case

J.H. is a 14-year-old with autism who presented to the emergency department for evaluation because he fell off the school bus. J.H.'s mother reports that recently he has been keeping his eye closed and he has been walking with his arms outstretched. J.H. was born full-term and has no other health conditions except for autism. J.H.'s diet consisted of crackers and chips only, and he was not taking any vitamins or supplements. On physical examination, J.H. looked underweight (body mass index, 13 [<5th percentile for age and sex]) and was agitated. Results of a head computed tomographic (CT) scan and a lumbar puncture were negative, so J.H. was discharged. On follow-up with his primary care doctor, bilateral corneal lesions were noted, so J.H. was referred for an urgent ophthalmology evaluation. J.H. was diagnosed as having xerophthalmia and corneal ulcers secondary to vitamin A deficiency. J.H. was treated with high-dose vitamin A. Two years later, on ophthalmology follow-up he was noted to be able to see objects and ambulate without assistance, but he had complete opacification of his left cornea and a corneal scar in his right eye.

Sources and DRIs

Vitamin A is the collective name for a family of fat-soluble compounds referred to as retinoic acids. There are 2 forms of dietary vitamin A. Preformed vitamin A is found in supplements and food from animal sources, such as fortified dairy products and liver. Provitamin A carotenoids are dietary precursors of retinol. The most important provitamin A carotenoid is β-carotene, which is found in carrots, broccoli, squash, peas, spinach, and cantaloupe. (3)

The RDAs for vitamin A are given as micrograms of retinol activity equivalents (RAEs) to recognize the different bioactivities of retinol and β-carotene. However, food and supplement labels state vitamin A levels in International Units. (3)

TABLE 1. Clinical and Laboratory Indicators of Selected Nutritional Deficiency States

FINDING	SUSPECTED MICRONUTRIENT DEFICIENCY
Skin	
• Dry skin (xerosis)	Vitamin A
• Petechiae, purpura	Vitamin C or vitamin K
• Ecchymosis, mucosal bleeding	Vitamin C or vitamin K
• Perioral and perianal rash	(Zinc)
• Poor wound healing	Vitamin C, (zinc)
Eyes	
• Bitot spots	Vitamin A
• Keratomalacia, conjunctival xerosis	Vitamin A
Mouth	
• Stomatitis and/or glossitis	Vitamin B_{12}, folate
• Bleeding and swollen gums	Vitamin C
Skeletal	
• Genu varum or valgum	Vitamin D
• Epiphyseal widening (especially wrists)	Vitamin D
• Costochondral beading	Vitamin D
• Bone pain	Vitamin C, (vitamin A toxicity)
• Refusal to walk, joint swelling	Vitamin C
Neurologic	
• Sensory loss	Vitamin B_{12}, vitamin E
• Ataxia	Vitamin B_{12}, vitamin E
• Loss of deep tendon reflexes	Vitamin B_{12}, vitamin E
Anemia	
• Microcytic	(Iron)
• Macrocytic	Vitamin B_{12}, folate
• Hemolytic	Vitamin E

Micronutrients in parentheses are not covered in this article.

When reading supplement labels it is important to note that 1 μg RAE = 1 μg retinol = 2 μg β-carotene (supplement) = 12 μg β-carotene (dietary) = 3.3 IU. (3)

Infants aged 0 to 1 year require 400 to 500 μg RAE/d of vitamin A, with a UL of 600 μg RAE. Children aged 1 to 3 years require 300 μg RAE/d of vitamin A, with a UL of 600 μg RAE. Children aged 3 to 8 years require 400 μg RAE/d of vitamin A, with a UL of 900 μg RAE. Children aged 9 to 18 years require 600 to 900 μg RAE/d of vitamin A, with a UL of 1,700 to 2,800 μg RAE. (3)

Functions

Vitamin A plays a critical role in vision, immunity, and cell differentiation and growth. In the vitamin A–dependent vision cycle, 11-cis-retinal, a derivative of vitamin A, combines with a membrane protein in the retina called opsin to form rhodopsin. Rhodopsin absorbs light and enables the transmission of its stimuli to the brain. Vitamin A is essential to the integrity of the cornea and conjunctiva as well as many other organs because of its importance for cell differentiation. (5)

Factors and Consequences of Vitamin A Deficiency

Xerophthalmia is the term used to describe the ocular manifestations of vitamin A deficiency. Night blindness is the earliest symptom and it is normally a sensitive and specific indicator for vitamin A deficiency. Patients with night blindness cannot see well at night or in dim light, and this can be difficult to recognize, especially among toddlers. Mild cases of night blindness can become apparent only after exposure to a bright light that depletes the limited stores of 11-cis-retinal in the affected patient. Night blindness responds to vitamin A therapy within 24 to 48 hours. If untreated, it leads to keratinization of the surface of the conjunctivae and, thus, is the histopathologic picture of conjunctival xerosis and Bitot spots that are characteristic for vitamin A deficiency. Bitot spots are generally whitish, foamy-appearing ovoid areas on the conjunctiva that result from a buildup of keratin. (6) Corneal xerosis and ulceration can develop in advanced eye disease and can subsequently lead to blindness. (7)

Before xerophthalmia is apparent, other serious consequences, including increased mortality, result from subclinical vitamin A deficiency. The protective effect of vitamin A against infant morbidity and mortality is due to its vital role in enhancing the host immune functions at different levels. Its protective effect against diarrheal diseases is due to its vital role in sustaining the integrity of the intestinal mucosa. The positive effect of vitamin A in human immunodeficiency virus–infected children is due to increased T-cell lymphopoiesis. The therapeutic effects of vitamin A against measles are well validated and are attributed to enhanced antibody production. (8)

Without supplementation, measles can induce a decompensation of vitamin A status and is known to precipitate 25% to 50% of blinding xerophthalmia in Asia. In many parts of Africa, measles is considered the leading cause of childhood blindness. (7)

TABLE 2. Examples of Micronutrient Deficiencies that Are Associated with Selected Clinical Conditions

CLINICAL SCENARIO	NUTRITIONAL DEFICIENCY
Vegetarian diet	Vitamin B_{12}
Obesity	Vitamin D (iron)
Cystic fibrosis	Vitamins A, D, E, K, B_{12}
Inflammatory bowel disease, short gut syndrome	Folate, vitamin B_{12}, fat soluble vitamins (iron)
Celiac disease	Folate, vitamin B_{12}, fat soluble vitamins (iron, zinc)
Prolonged diarrhea	(Zinc)
Medications	
• Antacids	Vitamin D, (iron)
• Seizure medications	Vitamin D
• Corticosteroids	Vitamin D
• Methotrexate	Folate
• Sulfasalazine	Folate
• Trimethoprim	Folate
The breastfed toddler with limited complementary food	(Iron, zinc)
Predominantly breastfed infant or toddler, refusing to walk, growth plateau	Vitamin D
Exclusively breastfed newborn, symptoms of bleeding or altered mental status	Vitamin K
The use of unfortified goat milk in infants with limited complementary food.	Folate
Highly restrictive diet (autism, developmental delay, food allergies)	Depends on the diet Vitamin A is vulnerable as in the case in the vignette; vitamin C
Highly restrictive diet and refusal to walk	Vitamin C
Measles	Vitamin A
Severe protein-energy malnutrition	Vitamin A, vitamin D, (zinc, iron)

Micronutrients in parentheses are not covered in this article.

The American Academy of Pediatrics (AAP) recommends vitamin A supplementation for children 6 months to 2 years old who are hospitalized for measles. The recommended oral supplement dose is 100,000 IU (30,000 μg) for children 6 to 12 months old and 200,000 IU (60,000 μg) for children older than 1 year. (9)

Measles is one example of how seemingly unrelated disease states can alter an individual's vitamin A balance and lead to deficiency.

The role of vitamin A for maintenance of normal epithelial cell integrity in the lungs has been examined in relation to chronic lung disease of preterm infants. A recent systematic review concluded that vitamin A supplementation had a modest benefit on risk of death, oxygen requirement, and development of chronic lung disease. No benefit was found on neurodevelopment in the second year of life. Definitive recommendations were not supported by the data. (10)

In patients with protein energy malnutrition, vitamin A deficiency can develop not only secondary to low dietary intake but also due to the effect of malnutrition on the transport and storage of vitamin A. (7)

Young children in developing countries are especially vulnerable to and at risk for vitamin A deficiency due to their dependence on human milk, which can be deficient if the mother is deficient. Intestinal infections that impair vitamin A absorption and respiratory infections, such as tuberculosis, that increase metabolic demands make affected children the most vulnerable victims of xerophthalmia. The same factors can affect older individuals, such as refugees who experience unsanitary conditions and nutritional deprivation. (7)

Risk of Toxicity

Preformed vitamin A toxicity can be acute (a single or short-term doses of retinol ≥150,000 μg for adults and proportionally lower doses for children) or chronic (long-term exposure to daily doses ≥600 μg). The toxic effects are transient and are due to increased intracranial pressure (pseudotumor cerebri). Symptoms include headache, blurred vision, vertigo, and a bulging fontanelle in infants. (5) This has led the IOM to apply a large safety margin in recommending the ULs for vitamin A. This is specifically important for women of childbearing age whose intake of retinol should not exceed 2,800 to 3,000 μg/d due to the risk of teratogenicity. (3)

Isotretinoin (13–*cis*-retinoic acid), a medication used to treat severe acne, is a teratogen that is associated with common birth defects. Since 2006, the Food and Drug Administration (FDA) established the iPLEDGE program by which the prescribing and dispensing of isotretinoin is more tightly controlled in an effort to reduce inappropriate drug use and exposure to women of childbearing age.

VITAMIN B_{12} (CYANOCOBALAMIN)

Case

C.S. is a 7-month-old infant who presented with failure to thrive, progressive loss of milestones, and shaking movements (Fig 1). On physical examination on the day of admission she looked pale but was alert and had normal vital signs. Her length and weight were below the 5th percentile, and she appeared malnourished. She showed generalized hypotonia with constant tremors of her tongue and extremities. The remainder of her physical examination was normal, with no anomalies or organomegalies.

C.S. was exclusively breastfed. The mother was on a well-balanced diet with oral multivitamins, and she has previously breastfed C.S.'s 2 siblings, who were reportedly healthy. The mother's medical history was significant for Graves disease.

Results of a CT scan of her head were normal. Laboratory evaluation was notable for macrocytic anemia. The findings of macrocytosis triggered further evaluation of vitamin B_{12} and folate levels, and her level of vitamin B_{12} was found to be significantly low. The mother's level of vitamin B_{12} was undetectable. The mother was found to have intrinsic factor (IF) antibodies secondary to an autoimmune process triggered by Graves disease.

C.S. was treated with vitamin B_{12} and was reported to have a nearly normal developmental outcome at 2 years of age.

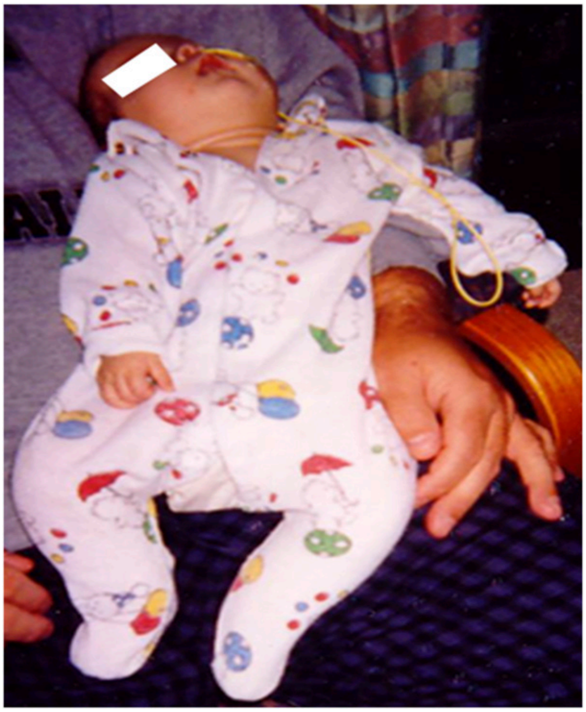

Figure 1. C.S. at 7 months of age presenting with marked hypotonia and loss of milestones.

Sources and Homeostasis of Vitamin B_{12}

Animal source foods such as milk, eggs, and meat are the only natural sources of vitamin B_{12}. (11) Absorption of the vitamin is distinctively complex, especially compared with other water-soluble vitamins. In the stomach, hydrochloric acid and pepsin release vitamin B_{12} from dietary protein, and cyanocobalamin is then bound to IF secreted by the gastric parietal cells. The complex B_{12}-IF remains intact until its uptake is facilitated by a specific receptor in the distal ileum. (12) Vitamin B_{12} deficiency can result from low dietary intake of animal source food due to cost, low availability, or religious and cultural beliefs. Dysfunction in any part of the sophisticated gastrointestinal pathway of cyanocobalamin absorption—from stomach to ileum—can lead to non–dietary-induced vitamin B_{12} deficiency.

The DRIs

The RDA for vitamin B_{12} is 0.9 μg/d for infants and toddlers, 1.2 to 1.8 μg/d for 4- to 13-year-olds, and 2.4 μg/d thereafter.

No adverse effects have been reported with excess vitamin B_{12} intake, and the risk of toxicity is very low; therefore, a UL is not established (3)

Maternal and Infant Vitamin B_{12} Deficiency

Most adults can tolerate a low vitamin B_{12} intake status for years without any clinical symptoms. Mothers of infants with vitamin B_{12} deficiency often have unrecognized pernicious anemia due to impaired vitamin B_{12} absorption, but other etiologies were reported, including gastric bypass surgery, short gut syndrome, or long-term vegetarian or vegan diet. (13) Newborn infants have limited endogenous stores and are at risk for vitamin B_{12} deficiency if they are predominantly breastfed, with a poor maternal vitamin B_{12} status and intake. (14) Typical manifestations usually start between 4 and 10 months of age and include growth faltering, developmental regression, tremors, hypotonia, lethargy, irritability, and feeding difficulties. (14) Megaloblastic anemia is not always present. (13)

Vitamin B_{12} replacement (1 mg intramuscular for 2 to 7 days [15]) leads to rapid recovery, with documented reversal of apathy, hypotonia, anorexia, and tremors within days of initiating treatment. Brain atrophy and growth failure reversed within several months. Unfortunately, despite the dramatic rapid improvement, many infants with vitamin B_{12} deficiency experience long-term cognitive and developmental delay. (14)

Similar symptoms are seen in infants with inborn errors of vitamin B_{12} absorption and utilization. A full discussion of these conditions is beyond the scope of this article.

Vitamin B_{12} Deficiency in Children and Adolescents

A study of serum B_{12} levels in 3,766 US children (4–19 years old) identified 3 children with levels less than 100 pg/mL (<74 pmol/L) (1 of 1,255) and 18 with levels less than 200 pg/mL (<148 pmol/L) (1 of 200). The highest incidence of children with levels less than 200 pg/mL (<148 pmol/L) was reported in the 12- to 19-year-old category, with a rate of 1 in 112. (15) Because the cutoff value suggested to define vitamin B_{12} deficiency is a level less than 203 pg/mL (<150 pmol/L), (11) these data indicate that B_{12} deficiency in children and adolescents is more common than previously suggested.

Of note, a vitamin B_{12} level greater than 300 pg/mL (>221 pmol/L) is tentatively considered as the cutoff value for B_{12} repletion. (16)

The estimated vitamin B_{12} intake in the United States is higher than the RDA, but dietary B_{12} deficiency is increasing due to atypical diets, such as extreme vegetarianism. (17) Patients who undergo gastric bypass or other bariatric surgeries are at risk for vitamin B_{12} deficiency due to the loss of gastric production of IF. (13) Pathologic disorders that disrupt the ileal length or surface, such as short gut syndrome, Crohn disease, and celiac disease, can affect B_{12} absorption. (15) It is especially important to note that previous and current use of gastric acid inhibitors for 2 or more years was significantly associated with the occurrence of vitamin B_{12} deficiency in adults. (18)

Neurologic changes secondary to B_{12} deficiency can occur without hematologic abnormality, including loss of deep tendon reflexes, developmental regression, hypotonia, and neuropsychiatric changes (eg, depression). (15)

Laboratory Evaluation

Several feasible indicators to assess vitamin B_{12} status are available, and the least expensive is a serum vitamin B_{12} level. (11) However, serum B_{12} level is not always reflective of tissue levels that can be depleted with a low normal or borderline serum cobalamin level. (15) Methylmalonic acid (MMA) and homocysteine are 2 precursors in the metabolic pathway and are affected by B_{12} deficiency. Homocysteine is elevated in both B_{12} and folate deficiencies, but an elevated MMA level is reasonably specific for B_{12} deficiency; MMA levels can be measured in both serum and urine. (13)

Studies are needed to determine the optimum strategy for the diagnosis of vitamin B_{12} deficiency in children. Several experts recommend B_{12}, MMA, and homocysteine levels when B_{12} deficiency is suspected. (13)(15) Once B_{12} deficiency is confirmed, subspecialty consultation, eg, a physician nutrition specialist, gastroenterologist, or hematologist, is recommended to guide further evaluation and treatment.

VITAMIN C (ASCORBIC ACID)

Introduction

In 1747, Dr James Lind, a surgeon in the British Navy, demonstrated that scurvy can be cured by consuming oranges and lemons. Since then, scurvy, or vitamin C deficiency, which used to debilitate sailors, has become a rare disease that warrants a case report. A recent one was published in the *New York Times* in July 2015. Although a clue to a disrupted eating pattern was clear on the initial presentation (the child has developmental delay and will eat only macaroni and cheese), a nutritional deficiency was not suspected. The patient had an extensive evaluation that included bone marrow biopsy and many subspecialist consults. This case is a testimony to the importance of physician knowledge about certain clues that should prompt a more detailed nutritional history.

Functions

Vitamin C is a water-soluble vitamin that acts as an antioxidant and free radical scavenger. Vitamin C is a cofactor for many enzymes and hormones and plays a major role in the biosynthesis of many components of connective tissue, such as collagen. It also modulates the absorption, transport, and storage of iron. (3)

The DRIs

The DRIs for vitamin C are based on estimates of tissue levels that are deemed adequate to provide antioxidant protection with minimal urinary loss. Tobacco smoking or environmental exposure to nicotine increases the vitamin C requirement by 35% to 40% due to increased oxidative stress. Vitamin C absorption in the small intestine is dose dependent, and the kidney also regulates its body content. As a result, excessive intake of vitamin C is unlikely to cause adverse effects other than gastrointestinal upset and osmotic diarrhea occasionally reported with large doses.

The RDA for vitamin C is 15 to 45 mg/d for children aged 1 to 13 years and 65 to 75 mg/d for those aged 14 to 18 years. (3)

Sources

Fruits and vegetables provide 90% of the vitamin C found in the typical diet. The major contributors are potatoes and citrus fruits and juices. (3) A diet that is persistently limited to meat, bread and/or dairy presents a high risk for inadequate vitamin C intake and development of deficiency.

Deficiency

Scurvy is rare in the current era but should not be forgotten. According to NHANES, children aged 6 to 11 years old had the highest mean serum concentration of ascorbic acid but showed a linear decrease thereafter. (19) In the pediatric population there are many case reports of scurvy in patients with autism due to their severely restrictive diet. Adults at risk for vitamin C deficiency include smokers, alcoholics, and those on a very restricted diet due to social isolation. (20)(21)

Clinical symptoms can develop only after 30- to 40 days of consuming a diet that is void of vitamin C. (22) The earliest symptoms of vitamin C deficiency are fatigue and refusal to walk. (20) Dermatologic findings include petechiae centered on hair follicles with hyperkeratosis and coiled hair. Hematomas, ecchymosis, poor wound healing, and edema may also be noted. Oral manifestations occur only in patients with teeth and include bleeding and hypertrophic gums. Musculoskeletal findings include joint pain, hemarthrosis, and muscle pain. Anemia is a common finding in vitamin C deficiency, and it can be attributed to the hemorrhagic symptoms and the role of ascorbic acid in iron absorption. (23) Infantile scurvy is rarely seen because human milk (if the maternal diet is sufficient) and formula provide an adequate supply of vitamin C. Infantile scurvy presents with bone abnormalities, bleeding, and anemia. (3)

High-Dose Vitamin C for the Treatment of Upper Respiratory Tract Infections

Supplementation trials have shown that vitamin C reduces the duration of colds, but this effect was not replicated in therapeutic trials. Further randomized controlled trials are warranted to investigate the role of vitamin C in the treatment of upper respiratory tract infections. However, given its low cost and excellent safety profile, it may be worthwhile for patients with common cold to try a therapeutic dose of vitamin C. (24)

VITAMIN D (CHOLECALCIFEROL)

Introduction

Rickets has plagued children, especially in the northeastern United States, since the 1800s. However, the beneficial effect of sunlight was not elucidated until 1921 when Hess and Unger reported a dramatic improvement in rachitic children who were exposed to the sun. (25) Contemporaneously, investigators observed that ultraviolet irradiation of milk and various foods imparted antirachitic activity. With this discovery it was thought that rickets was conquered. (25) However, in the 19th century it became clear that vitamin D deficiency is a common problem in children and adults worldwide. In fact, the discovery that various cells and tissues express the vitamin D receptor has highlighted its many other nonskeletal functions. Now experts believe that rickets is simply only the "tip of the iceberg" of the consequences of vitamin D deficiency. (26)

Case

J.L. is a 15-month-old white boy who fell off his bed and refused to walk afterward. He had been walking for about a month before this episode. His dietary history showed that he was breastfed until 6 months of age and then was placed on a mostly liquid diet consisting of water, juice, and some milk. Solids in his diet consisted of some baby food without dairy products. No supplemental vitamins were given.

Physical examination was significant for underweight status (weight-for-length <5th percentile), length age of 9 months (his length was 70.6 cm), a prominent forehead, and swelling at the wrists. Radiographs of his leg revealed a distal left femur fracture, and wrist radiographs showed osteopenia with metaphyseal flaring.

Laboratory studies showed a low-normal serum calcium level of 8.2 mg/dL (2.05 mmol/L), a low serum phosphorus level of 3.4 mg/dL (1.1 mmol/L), but elevated alkaline phosphatase and parathyroid hormone (PTH) levels. The serum 25-hydroxyvitamin D (25[OH]D) level was low at 11 ng/mL (27 nmol/L).

J.L. was given stoss therapy with a high dose of vitamin D (100,000–600,000 IU given over 1–5 days). The appearance of his wrist at 1 and 5 months of age showed gradual healing of his rickets (Fig 2).

Definition of Vitamin D Deficiency

There continues to be much debate regarding what constitutes vitamin D deficiency, insufficiency, and sufficiency. Vitamin D status is defined by the level of serum circulating 25(OH)D. (27)(28)

The Endocrine Society proposed the following cutoff points (27):

- Vitamin D deficiency: 25(OH)D level ≤20 ng/mL (<50 nmol/L)
- Vitamin D insufficiency: 25(OH)D level of 21 to 29 ng/mL (52–72 nmol/L)
- Vitamin D sufficiency: 25(OH)D level of 30 to 100 ng/mL (75–250 nmol/L)

The Endocrine Society determined these cutoff points using many criteria that affect bone metabolism, such as PTH, bone mineralization, and intestinal calcium absorption.

However, to establish vitamin D requirements through the life cycle at a population level, the IOM prioritizes specific end points associated with health outcomes. Accordingly, the IOM has questioned the premise that a serum level of 25(OH)D greater than 30 ng/mL (>75 nmol/L) provides additional health benefits. (29) At present, the IOM, the AAP, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition also suggest 20 ng/mL(50 nmol/L) as the cutoff value for deficiency, (30) but the controversy continues regarding the level of serum 25(OH)D that defines sufficiency.

Prevalence of Vitamin D Deficiency

Vitamin D deficiency is widespread around the world. (27) The NHANES studies examined thousands of American children and adolescents, which provides a reliable report of their vitamin D status. According to NHANES 2001–2004, 9% of US children and adolescents had vitamin D deficiency (25[OH]D levels <15 ng/mL [<37 nmol/L]), and 61% had vitamin D insufficiency (25[OH]D levels of 15–29 ng/mL [37–72 nmol/L]). (31)

Causes and Risk Factors for Vitamin D Deficiency

Limited Sunlight Exposure. When absorbed by the skin, UV-B converts 7-dehydrocholesterol to previtamin D_3, which is isomerized to vitamin D_3.

There are many factors, such as skin pigment and use of sun screen, that influence the cutaneous production of vitamin D_3. Increased skin pigmentation causes the melanin to absorb most of the UV-B, resulting in much lower vitamin D_3 production in African American individuals compared with white individuals for the same UV-B exposure. Sunscreen with a sun-protecting factor of 30 can reduce the skin's ability to produce vitamin D by 95% to 99%. The influence of these factors is exacerbated by the season, latitude, and time of day. When the zenith angle of

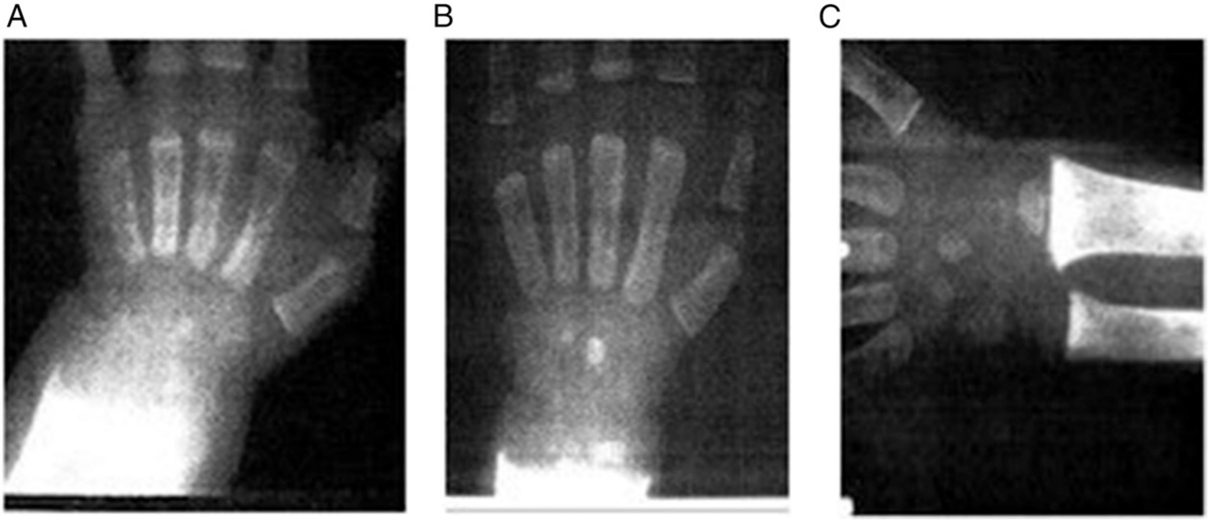

Figure 2. J.L. wrist radiographs from left to right: at presentation and 1 and 5 months after treatment. Notice the swelling at the wrist.

the sun is more oblique during the winter season (especially far north and south) and for the daylight hours before 10 AM and after 3 PM, more UV-B radiation is absorbed by the ozone layer. Passage through glass or plastic and air pollution also dramatically reduces UV-B. (32)

Limited Nutritional Intake in Infancy and Beyond. Breastfed infants and toddlers are at risk for vitamin D deficiency. The content of vitamin D in human milk is greatly influenced by all the factors that affect maternal vitamin D status, such as sun exposure, skin pigmentation, season, latitude, and maternal vitamin D intake. The optimal vitamin D supplement dose for nursing mothers is not yet established. However, studies have shown that maternal supplementation of vitamin D at 4,000 IU/d was not enough to consistently yield at least 400 IU of vitamin D per liter of human milk. It is hypothesized that a supplemental dose of 6,000 IU/d may be needed to achieve this effect. This should not undermine the value of human milk as a vital source of nutrition for infants but highlights the basis for the recommendation to supplement all infants who are breastfeeding or taking less than 1 L of formula per day with 400 IU of vitamin D daily. (33)(34)

Beyond the first year of life, an intake of 32 oz of vitamin D–fortified milk provides 400 IU of vitamin D. Fatty fish and other vitamin D–rich foods tend to be absent in most infant and adolescent diets, and the content of vitamin D in fortified foods may be overestimated. For example, fortified cereal provides only 40 IU per serving. Thus, for children and adolescents who do not receive regular sunlight exposure, they may be at increased risk for nutritional vitamin D deficiency and insufficiency. (35)

The Effect of Obesity. The association between obesity and lower 25(OH)D serum concentration is well established. Possible mechanisms include lower dietary intake, sedentary behavior that tends to limit sunlight exposure, and sequestration of 25(OH)D in the adipose tissue. (36)

Medications. Antiepileptic drugs and systemic glucocorticoids have been shown to reduce 25(OH)D concentrations when dietary sources of vitamin D and sunlight exposure are limited. Of note, there is no evidence that inhaled corticosteroids at a conventional dose given for 2 to 3 years have a negative effect on bone mineral density and bone turnover biomarkers, including 25(OH)D. (37)

Orlistat and cholestyramine cause fat malabsorption and, thus, impair vitamin D absorption. (38)

Diseases that Interfere with Vitamin D Absorption and Metabolism. Vitamin D absorption is chylomicron dependent; thus, children with fat malabsorption are at increased risk for deficiency. Cystic fibrosis, Crohn disease, and celiac disease are known risk factors for nutritional rickets. (38) Food allergies and small-bowel resection can also lead to fat malabsorption and vitamin D deficiency. (35)

Genetic Factors. In a study published in the *New England Journal of Medicine,* Powe et al report that more than 90% of African American individuals have a genotype that is associated with a lower level of vitamin D–binding protein compared with white individuals. (39) The authors speculate that variation in vitamin D–binding protein levels may be responsible for observed racial differences in 25(OH)D levels and the clinical manifestations of vitamin D deficiency. (39) More research is needed to elucidate if genetic polymorphism plays a role in determining vitamin D requirements in different ethnic groups.

Skeletal Consequences of Vitamin D Deficiency

A vitamin D–deficient state is associated with reduction in intestinal calcium absorption from approximately 30% to 40% to 10% to 15%. The body responds to the reduction in serum calcium with hyperparathyroidism. (35)

Parathyroid hormone enhances calcium absorption in the renal tubules. It also causes phosphaturia, leading to a low serum phosphorus level that causes a maturation defect in the chondrocytes with cellular ballooning and disruption of the growth plate, leading to the widening at the end of the long bones that is characteristic of rickets. (35)

Rickets can be divided into 3 stages (Fig 3). The first stage is characterized by osteopenia and subclinical hypocalcemia. Bone pain and rachitic changes start in the second stage and become progressively worse in the third stage. (35)

Clinically, rickets in children ranges from an asymptomatic disease to varying degrees of poor growth, bone pain, irritability, and gross motor delay.

The signs of rickets include, but are not limited to, genu varum (bowing of the legs) or genu valgum (knock-knees), due to the lack of structural support as the child learns to walk. The widening at the end of the long bones is most commonly manifested in the wrist. The *rachitic rosary* is a term used to describe the beading along the anterior chest wall and is a result of the hypertrophy of the costochondral joints. (25)(35)

In rare cases of severe maternal vitamin D deficiency, rickets can develop in utero. (33)(34)

Nonskeletal Consequences of Vitamin D Deficiency

Every cell and tissue in the body has a vitamin D receptor. Therefore, vitamin D deficiency has been associated with a plethora of negative health consequences. (25)(40) Maternal vitamin D deficiency is associated with low birthweight (33) and is linked to increased risk of preeclampsia. (25)(40)

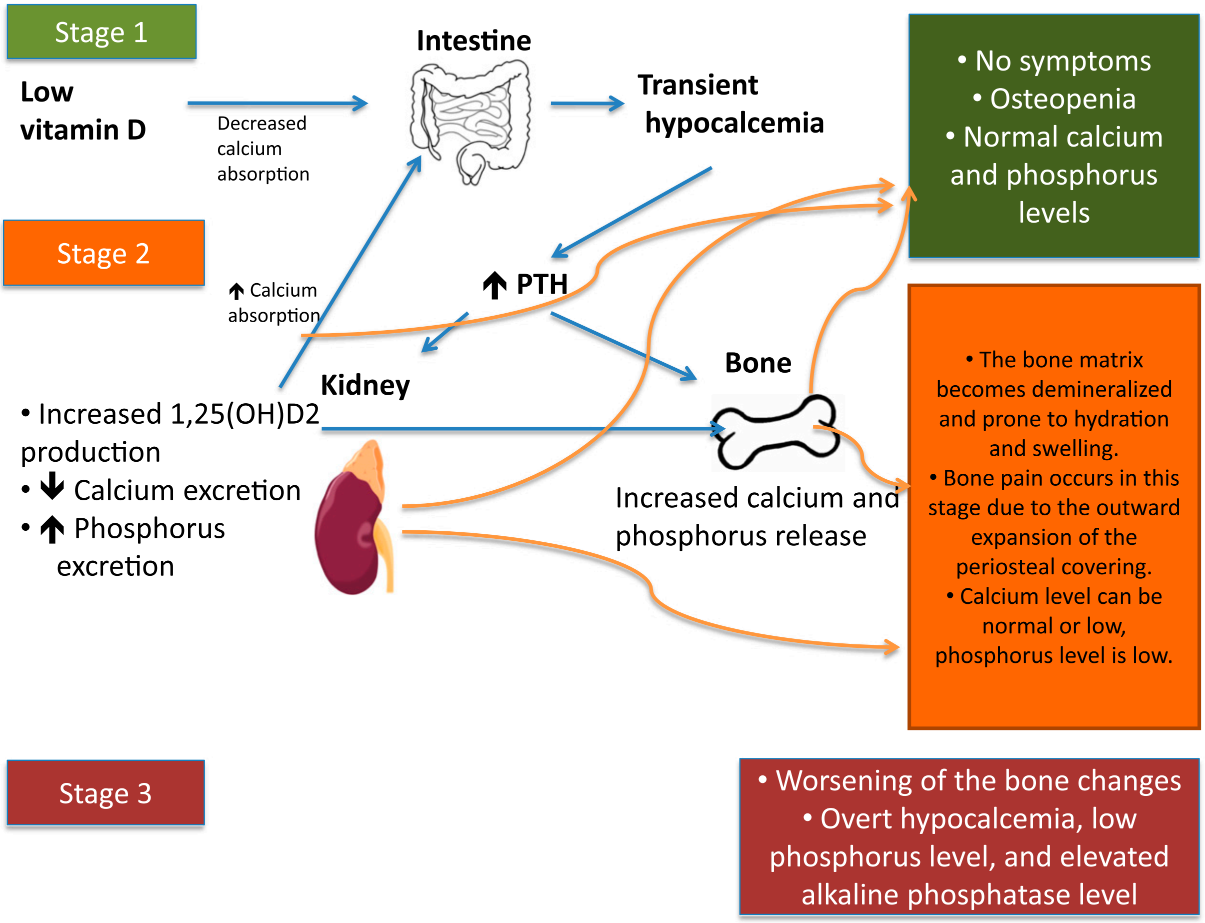
Stage 1
Low vitamin D
Decreased calcium absorption
Intestine
Transient hypocalcemia
• No symptoms
• Osteopenia
• Normal calcium and phosphorus levels
Stage 2
↑ Calcium absorption
↑ PTH
Kidney
Bone
• Increased 1,25(OH)D2 production
• ↓ Calcium excretion
• ↑ Phosphorus excretion
Increased calcium and phosphorus release
• The bone matrix becomes demineralized and prone to hydration and swelling.
• Bone pain occurs in this stage due to the outward expansion of the periosteal covering.
• Calcium level can be normal or low, phosphorus level is low.
Stage 3
• Worsening of the bone changes
• Overt hypocalcemia, low phosphorus level, and elevated alkaline phosphatase level

Figure 3. Stages and skeletal consequences of vitamin D deficiency. PTH=parathyroid hormone; 1,25(OH)2D=1,25 dihydroxyvitamin D.

Vitamin D deficiency has also been linked to increased risk of infectious disease, types 1 and 2 diabetes, multiple sclerosis, cardiovascular disease, dementia, and cancer, (40)(41) but controlled trials to determine causality are not available.

Laboratory Evaluation of Vitamin D Status

Circulating 25(OH)D level measured by a reliable assay is the best indicator of vitamin D status and stores. Measurement of serum 1,25 dihydroxyvitamin D (1,25[OH]2D) is not recommended because 1,25(OH)2D does not reflect vitamin D reserves and can be normal or elevated in patients with vitamin D deficiency due to secondary hyperparathyroidism. Measurement of the 1,25(OH)2D level is useful in conjunction with the PTH level in disorders of 25(OH)D and phosphate metabolism, such as chronic kidney disorders and vitamin D–resistant rickets. (27) In nutritional rickets, the classic biochemical profile includes the triad of hypocalcemia, hypophosphatemia, and elevated alkaline phosphatase levels.

Some experts recommend incorporating the measurement of vitamin D–binding protein for better assessment of vitamin D status in African American individuals and in diverse populations, (39) but more research is needed.

Screening

Universal screening of all patients for vitamin D deficiency is not recommended (27) and should be reserved and considered only for high-risk patients, including but not limited to:

- Patients with nonspecific symptoms, such as poor growth, irritability, and gross motor delay (35)
- Dark-skinned patients, especially those who live in higher latitudes (27)(35)
- Children taking long-term glucocorticoids or seizure medications (27)(35)
- Children with chronic diseases that are associated with fat malabsorption, such as cystic fibrosis, inflammatory bowel disease, (35) and post–bariatric surgery (27)

- Patients with frequent fractures and low bone density (35)
- Patients with chronic kidney disease (27)
- Obese patients (27)

Screening can also be considered for patients with low dietary intake and very limited sun exposure.

Sources and Forms of Vitamin D

There are 2 sources of vitamin D. Cholecalciferol (D_3) is synthesized in the skin and found in oily fish. Ergocalciferol (D_2) is synthesized by plants and produced from the irradiation of yeast. Both forms are used to fortify milk and are found in dietary supplements, but vitamin D_2 is the only prescription form available in the United States. (33)(42) Table 3 summarizes the pharmaceutical and supplemental sources of vitamin D.

Calcidiol (25[OH]D), the form that defines vitamin D status, is formed in the liver from vitamins D_2 and D_3 by the action of 25-hydroxylase. Calcitriol (1,25[OH]2D), the active form of vitamin D, is created when a second hydroxylation occurs in the kidney and many other tissues in the body. (33)(42)

Treatment of Vitamin D Deficiency

There are many strategies to treat vitamin D deficiency. Based on studies that examine the effect of D_2 and D_3 administered in different doses on 25(OH)D serum level, experts estimate that 100 IU of vitamin D_2 or D_3 daily will raise the blood level of 25(OH)D by 1 ng/mL (2.5 nmol/L). (25)(26) Short-term administration of 2,000 IU of vitamin D_2 or D_3 daily yields an equivalent outcome to weekly 50,000 IU of vitamin D_2. (27)(43) Thus, pediatricians can individualize their treatment of vitamin D to meet the patients' and families' preferences and probability of compliance. When compliance is a major concern, stoss therapy (*stoss* in German means to push), with doses of 100,000 to 600,000 IU given over 1 to 5 days, can be administered to infants older than 1 month of age. (35) However, the recommendations of the stoss therapy, especially in outpatient settings, have been met with controversy due to the risk of hypercalcemia. (43)

In July 2011, the Endocrine Society published the following guidelines for the evaluation, treatment, and prevention of vitamin D deficiency (27):

- Infants 0 to 1 year old: 2,000 IU orally once daily or 50,000 IU orally once weekly for 6 weeks until the 25(OH)D blood level is greater than 30 ng/mL (>75 nmol/L), followed by maintenance therapy (400–1,000 IU/d)
- Children 1 to 18 years old: 2,000 IU orally once daily or 50,000 IU orally once weekly for 6 weeks until the blood level is greater than 30 ng/mL (>75 nmol/L), followed by maintenance therapy (600–1,000 IU/d)
- Use of a high dose (double or triple the 2 previously mentioned doses) is recommended for obese patients or patients taking medications or having conditions that affect vitamin D metabolism and/or absorption

Prevention of Vitamin D Deficiency: The DRIs and Other Recommendations

The AAP recommendations on vitamin D supplementation are in agreement with the IOM recommendations released in 2011. The IOM proposed that healthy infants younger than 1 year of age consume 400 IU/d of vitamin D, and older children (1–18 years old) consume 600 IU/d. (35)(44)

Dietary Sources of Vitamin D. Many children and adolescents in the United States do not consume most of the natural food sources of vitamin D in sufficient quantities. Furthermore, meeting the RDA of vitamin D would require an impractically large intake of fortified food. For example,

TABLE 3. **Summary of Supplemental and Pharmaceutical Sources of Vitamin D (26)**

VITAMIN D SUPPLEMENT	DOSE	NOTES
Prescription		
• Vitamin D_2 (ergocalciferol, labeled calciferol)	Capsule: 50,000 IU Liquid: 8,000 IU/mL	For small children, the capsule can be soaked in water to soften it, then given intact with blended food such as apple sauce (35)
Over the counter		
• Pediatric multivitamin (liquid or chewable)	300, 400, 600 IU D_2 or D_3	D_3 400 IU/mL is the standard to use (1 mL/d) for prevention of vitamin D deficiency in newborns and toddlers who are breastfeeding or taking <1,000 mL/d of formula/whole milk. It is available over the counter under many brand names.
• Vitamin D_3 (labeled cholecalciferol)	400, 800, 1,000, and 2,000 IU	

TABLE 4. **Diagnostic Tests and Treatment Doses for Selected Vitamin Deficiencies**

VITAMIN	DIAGNOSTIC LABORATORY TEST	TREATMENT
Vitamin A	Serum retinol <20 μg/dL Molar ratio of retinol to retinol binding protein <0.8 (calculated in μmol/L) (75)	■ Infants <6 mo old: 50,000 IU orally × 1 ■ Infants 6–12 mo old: 100,000 IU orally × 1 ■ Children >12 mo old: 200,000 IU orally × 1 (76) Additional doses can be given, as needed, every 4 weeks based on clinical response.
Vitamin B_{12}	Use serum B_{12} as the initial test; if the level is <271 pg/mL (<200 pmol/L), check for elevated methylmalonic acid level (>0.37 μmol) (16)	• Dietary deficiency: Infants (breastfed by vitamin B_{12}–deficient mothers): IM 250–1,000 μg once daily for 1–2 wk, then weekly until recovery • Malabsorption: Infants, children, and adolescents: IM 250–1,000 μg/d or every other day for 1 wk, then weekly for up to 8 wk, and then every 4 wk; oral administration of a high dose of 2,000 μg/d can also be considered (16)
Vitamin C	Plasma and leukocyte vitamin C level (77)	Scurvy: Oral, IM, IV, SC: Initial: 100 mg per dose 3 times daily for 1 wk (300 mg/d) followed by 100 mg once daily for 1–3 mo (47)
Vitamin E	Serum α-tocopherol and serum α-tocopherol to lipid ratio (47)	Fat malabsorption: Supplement with 25 IU/kg per day to prevent deficiency (47)
Folate	Serum homocysteine level elevated (also elevated in B_{12} and B_6 deficiencies) (47)	Oral daily administration of 0.1 mg in infants and 1 mg in children followed by oral daily maintenance of 0.1–0.5 mg (47) Note that treatment for folate deficiency without assessment of vitamin B_{12} status can mask B_{12} deficiency
Vitamin K	Prothrombin time is elevated (4 times normal) and the presence of protein induced by vitamin K deficiency (73)	• Prevention: A singe 1-mg IM dose for the full-term infant and 0.3–0.5 mg for the preterm infant • Fat malabsorption: 2.5–7 mg/d 2–7 times per week (47)

IM=intramuscular, IV=intravenous, SC=subcutaneous.

a 15-year-old must consume a pound of cheese or 6 glasses of milk per day to obtain the recommended 600 IU of vitamin D daily.

Good natural food sources of vitamin D include salmon (100–1,000 IU of vitamin D per 3.5 oz) and cod liver oil (400–1,000 IU of vitamin D per 1 tsp). (26)

Preventive Use of Supplemental Vitamin D. Taking into consideration the IOM and AAP recommendations for the general population and the Endocrine Society focus on high-risk patients, the following key points are proposed in guidelines and experts' statements:

- Vitamin D supplementation is recommended for all young infants regardless of the type of feeding because it takes 1 L of formula to provide 400 IU of vitamin D (33)
- Vitamin D supplementation should be started within the first days after birth (33)
- Recommended vitamin D supplement intake for children and adolescents without risk factors for vitamin D deficiency are 400 IU/d during the first year and 600 IU/d for children 1 to 18 years old (33)(44)
- Recommended vitamin D intakes for infants, children, and adolescents with risk factors for deficiency are 400 to 1,000 IU/d during the first year and 600 to 1,000 IU/d for children 1 to 18 years old (30)
- For preterm infants the recommended vitamin D intake is 400 to 800 IU/d (30)
- The optimal duration of vitamin D supplementation has not yet been established; it is reasonable to consider supplementing while the growth velocity is high, until age 2 years (30)
- In children older than 2 years of age, vitamin D supplementation should be based on risk factors, dietary intake, and sun exposure; a supplemental dose of 400 IU/d is recommended for children and adolescents who do not obtain such a dose from fortified milk (33)
- Children with limited summer sun exposure may be supplemented in the late fall and winter (30)
- Obese children or patients taking anticonvulsants or glucocorticoids should receive at least 2 to 3 times more vitamin D than children without such risk factors (27)(30)
- Pregnant and lactating women require 600 IU/d of vitamin D; a dose of 1,500 to 2,000 IU/d may be needed

to maintain the 25(OH)D serum level greater than 30 ng/mL (>75 nmol/L) (27)

Sensible Sunlight Exposure. Human skin has a wonderful capacity to produce vitamin D_3, which is stored in the fat tissue and released during the winter months. Sensible sun exposure, defined by the exposure of the arms and legs without sunscreen for 5 to 30 minutes between 10 AM and 3 PM twice a week, is often adequate. (26)(45)

Toxicity

Excessive intake of vitamin D can cause hypervitaminosis D and results in hypercalcemia and hypercalciuria. (28) However, vitamin D intoxication is rare, and the cases reported were the result of inadvertent ingestion of extremely high doses of vitamin D for prolonged periods. (32) Sunlight exposure never causes vitamin D intoxication. (32) The UL of vitamin D intake should not exceed 1,000 IU for infants 0 to 12 months old and 2,000 IU for older children (28) unless deficiency has been documented and therapy is being monitored.

VITAMIN E (TOCOPHEROL)

Vitamin E is a fat-soluble antioxidant that protects the cells from the damaging effects of free radicals. Cell damage due to free radicals has been linked to the development of cardiovascular disease and cancer.

Structure, Sources, and the DRIs

Vitamin E is abundant in many food sources, such as fruits, vegetables, meats, grains, and vegetable oils. Vitamin E is also available as a dietary supplement. Naturally occurring vitamin E exists in 8 forms (α-, β-, γ-, and δ-tocopherols and tocoretinols). α-Tocopherol is the only form recognized to meet human requirements and is the form referred to in the DRIs as set by the IOM. (3)

Adequate intake of vitamin E in the first year of life is 4 to 5 mg/d of α-tocopherol. The RDA of vitamin E for children aged 1 to 8 years is 6 to 7 mg/d of α-tocopherol, with a UL of 200 to 300 mg. The RDA of vitamin E for children aged 9 to 13 years is 11 mg/d of α-tocopherol, with a UL of 600 mg. The RDA for age 14 years through adulthood is 15 mg/d of α-tocopherol, with a UL of 800 to 1,000 mg. (3)

Vitamin E Deficiency

Because of its abundance in natural sources, vitamin E deficiency is rare and generally occurs as a result of fat malabsorption syndromes or in the setting of protein energy malnutrition. The main clinical symptom of vitamin E deficiency is peripheral neuropathy with ataxia and hyporeflexia. (3)(46) Patients with malabsorption (cystic fibrosis, pancreatic insufficiency) and biliary tract disorders are at risk for vitamin E deficiency. Failure to supplement high-risk patients leads to a progressive neurologic disorder, including ataxia, peripheral neuropathy, proximal muscle weakness, and ophthalmoplegia. These effects may be irreversible if the deficiency is longstanding. (47)

Risk of Toxicity

Supplements of vitamin E provide α-tocopherol with amounts that are more than or equal to 100 IU. These amounts are significantly higher than the RDAs. The possible effects of a high supplemental level of α-tocopherol remain uncertain. However, some adult studies suggest that the use of high doses of vitamin E may increase all-cause mortality. (48)

Vitamin E supplement use is high in the US population. The most frequently reported motivation for use was to improve overall health. (49) The 1986 National Health Interview Survey reports that supplements containing vitamin E are used by 37% of young children in the United States. (3) Excess vitamin E intake in individuals who are deficient in vitamin K or receiving anticoagulant therapy can lead to hemorrhagic toxicity. (3)

There is no evidence of adverse effects from exposure to high levels of the vitamin E naturally occurring in foods. (3)

Therapeutic and Preventive Use of Vitamin E

Using pharmacologic doses of vitamin E as an antioxidant has been proposed for the treatment or prevention of many diseases. Vitamin E supplementation in preterm infants reduced the risk of intracranial hemorrhage (ICH), and in the very low-birthweight infant it also reduced the risk of severe retinopathy. (50) However, the current evidence does not support the routine use of vitamin E supplementation intravenously in high doses due to the increased risk of sepsis. (51)

Several studies investigated the role of vitamin E and the reduction of oxidative stress in the treatment of nonalcoholic steatohepatitis (NASH) and have led to variable results. (52)(53)(54)

One of the largest studies in adults (247 patients) concluded that vitamin E at a dose of 800 IU/d was superior to placebo in the treatment of NASH in nondiabetic adults. (55) The same dose is proved to offer histologic benefits to children with biopsy-proven NASH, but more studies are needed before its use can be recommended in pediatrics clinical practice. (56)

Vitamin E may have functions that are not related to its role as a free radical scavenger. Vitamin E has a positive effect on the immune system and a possible protective effect against upper respiratory tract infection. Vitamin E also has anti-DNA mutagenic damage properties that may explain its protective effects against cardiovascular diseases, Alzheimer disease, and cancer. (5)

FOLATE (PTEROYLPOLYGLUTAMATE)

Introduction

In 1931, Dr Lucy Willis demonstrated that a factor in yeast, subsequently shown to be folate, cured megaloblastic anemia of pregnancy. (57) In the 87 years since that original discovery, the roles of folate in the pathogenesis of neural tube defects (NTDs), vascular disease, and certain types of cancer have been established.

Sources and the DRIs

The term *dietary folate* is used to denote folate that occurs naturally in food sources and the more active synthetic form of folic acid used in fortified food. *Total folate* is an umbrella term used to encompass all dietary and supplemental exposure to folate and folic acid. (58)

Rich food sources of folate include dark green vegetables, beans, and legumes. (3) However, the food retention of folate is highly dependent on the type of food and the method of cooking. Folate from animal sources is more stable than folate in green vegetables, and steaming is superior to boiling for folate retention. (59) This has led to public health efforts to increase folic acid intake on a population level, especially since the finding that folic acid supplementation in the preconception period unequivocally decreases the incidence of NTDs. (60) The FDA authorized the addition of folic acid to enriched grain products in March 1996, with compliance mandatory by January 1998. (61) This resulted in a dramatic decrease in folate deficiency and NTDs. (61)(62)

The RDA of folate is 150 μg/d for the first 3 years after birth, then 200 to 300 μg/d for 4 to 13 years old and 400 μg/d thereafter. The RDA for pregnant women is 600 μg/d. The UL applies to folic acid from fortified food and supplements and ranges from 300 to 1,000 μg/d. (3)

Causes and Metabolic Indicators of Folate Deficiency

Isolated folate deficiency is rare; it is often associated with conditions that affect other nutrients. Small-bowel disorders associated with malabsorption, such as inflammatory bowel disease and celiac disease, can cause folate deficiency. Pregnancy, lactation, and chronic hemolytic anemia increase folate requirements. Other populations at risk for folate deficiency include premature infants and alcoholics. (46) Infants consuming unfortified goat milk have classically been found to develop folate deficiency, manifesting as macrocytic anemia.

Several medications, such as methotrexate and trimethoprim, act as folate antagonists and produce a deficiency by inhibiting dihydrofolate reductase. Other medications that can lead to folate deficiency include anticonvulsants, antituberculosis drugs, and oral contraceptives, but the mechanism is unclear. (46)

Serum or erythrocyte concentrations of folate are reasonable indicators of this vitamin status. Serum levels reflect relatively recent intake and can respond quickly; erythrocyte levels may be preferred as an indicator of chronic intake. Both MMA and homocysteine assays obtained in the setting of megaloblastic anemia help differentiate between B_{12} and folate deficiency. Both are elevated in B_{12} deficiency, but only homocysteine is increased in folate deficiency. (11)

Correction of macrocytic anemia with folate can mask an underlying B_{12} deficiency and will allow progression of neurologic damage due to the latter. It is, thus, critical to distinguish folate vs B_{12} deficiency before initiating treatment.

Heath Consequences of Folate Deficiency

A decline in serum folate level occurs in approximately 2 weeks of consumption of a folate-deficient diet, and megaloblastic anemia occurs within weeks if the deficiency continues. (11)

The effect of maternal folate status on pregnancy outcome is indisputable. There is a strong association between low maternal folate status and increased risk of NTDs. However, the association between folate status and the risk of other birth defects, such as cleft palate, is not as strongly established. (11)

There is also strong evidence of an inverse association between blood folate concentration and the risk of low birthweight. (11)

In adults, there is moderate evidence that low folate concentration is associated with a higher prevalence of depression, cognitive impairment, and dementia. The association between folate status and cognitive function is weaker in children. (11)

Folate and Chronic Disease Prevention

Folate plays an important role in DNA synthesis and repair, but the research about its effect on carcinogenesis and cancer prevention has been contradictory, and this has led to its being called a double-edged sword. Earlier studies suggested that the use of folate in adults can reduce the risk of colon cancer in women and men. (63)(64) However, randomized controlled trials did not confirm this effect and raised the possibility of a cancer-promoting effect. (65) More research is needed from a public health perspective on the effect of folate on cancer risk and prognosis.

Folate was also postulated to play a protective role against cardiovascular disease because of its role in lowering the homocysteine level, (66) but randomized controlled trials did not provide any evidence to support this role. (67)

Risk of Toxicity

No adverse effects have been attributed to excessive consumption of folate from food. Excessive intake from supplemental folate may obscure and potentially delay the diagnosis and treatment of vitamin B_{12} deficiency, which can lead to neurologic damage. (3)

VITAMIN K (PHYTONADIONE)

In 1943, Dam and Doisy received the Nobel Prize in Medicine for elucidating the chemical structure of vitamin K. They named this fat-soluble compound K due to its role in "Koagulation."

Structure and Sources

Vitamin K belongs to a family of molecules that share a 2-methyl-1, 4-napthoquinone ring but differ in the identity of the side chain at the 3-position. Vitamin K is present in plants as phylloquinone and is produced by bacteria in human and animal large intestine as menaquinone. The significance of the gut microbial production of vitamin K is not clear because most of the absorption occurs in the small intestine. The small intestinal absorption of this liposoluble vitamin is enhanced by dietary fat but also depends on the flow of bile and pancreatic enzymes. Vitamin K is stored in the liver. (3)(5)

Dietary sources of vitamin K include green leafy vegetables such as spinach and collard greens, soy and canola oils, and margarine.

The DRIs

The data were insufficient to recommend an Estimated Average Requirement and an RDA for vitamin K. Adequate intake of vitamin K intake is 2 to 2.5 μg/d for infants and 30 to 75 μg/d for 1- to 18-year-olds. Others have recommended 1 μg/kg per day. (68) No adverse effects were reported from high vitamin K intake from food or supplements in healthy individuals who are not receiving anticoagulant drug therapy. The data were insufficient to establish a UL. (3)

Functions and Consequences of Vitamin K Deficiency

Vitamin K is a cofactor for γ-glutamyl carboxylase, the enzyme responsible for the modification of the side chain of some proteins from glutamate to γ-carboxyglutamate. Most γ-carboxylated proteins are clotting factors such as factors II (prothrombin) VII, IX, and X. This underlies the essential role of vitamin K in the coagulation cascade.

Other carboxylated proteins play an important role in calcium homeostasis and, thus, are important for bone and cardiovascular health. There is also emerging evidence about the protective effects of vitamin K against oxidative stress, age-related decline in motor and cognitive functions, cancer, and hepatitis C. (5)

Clinically relevant vitamin K deficiency is rare and is usually limited to patients with lipid malabsorption syndromes or those who take certain medications (such as antibiotics, vitamin A, and vitamin E) that interfere with vitamin K metabolism. (3) In this review, we focus on the importance of recognizing the recrudescence of vitamin K deficiency bleeding (VKDB), formerly known as hemorrhagic disease of the newborn.

Cases

A 6-week-old infant presented to a tertiary care center emergency department with a 1-day history of poor breastfeeding, increased crying, pallor, and a "full and hard" anterior fontanelle. The medical history was relevant for exclusive breastfeeding and no vitamin K prophylaxis at birth. A full sepsis evaluation was initiated, and due to the bloody cerebrospinal fluid and the altered mental status, a head CT was obtained, which demonstrated a large ICH. The infant was treated with neurosurgical evacuation of the hematoma and administration of anticonvulsant agents. He remained seizure free with therapy but had a right hemiparesis and significant developmental deficit 3 months after ICH.

This infant was 1 of 5 cases of late VKDB presenting to a tertiary care center in Tennessee between February and September 2013, raising concerns about an increased occurrence of late VKDB due to parental refusal of vitamin K prophylaxis at birth. All 5 infants were exclusively breastfed and did not receive vitamin K prophylaxis at birth. Their age range was 6 weeks to 5 months, and 2 of the infants were born at home. One of the infants presented with a gastrointestinal bleed, and the other 4 had ICH. Of those who presented with ICH, 3 had varying degrees of developmental delay on follow-up. (69)

Symptoms and Risk Factors for VKDB

Recognition of VKDB is critical for prompt diagnosis and urgent therapy. Vitamin K deficiency bleeding can be classified as early (<24 hours after birth), classic (2–14 days), and late (2–12 weeks but can be seen in infants up to 6 months old). Symptoms of VKDB range from mild "warning bleeds" (umbilical cord, gastrointestinal, or circumcision bleeding) to severe (ICH). (5)(69) It is important to note that warning bleeds proceed ICH by days to weeks. (70)

Newborn infants are at increased risk for VKDB for several reasons. First, the placental transfer of vitamin K is poor, and its half-life in the liver stores is short. Second, the newborn gut flora is immature and unable to produce vitamin K, rendering the newborn infant dependent on dietary intake as the main source of vitamin K. The exclusively breastfed infant is especially at risk for late VKDB because the human milk content of vitamin K is low; standard fortification of infant formulas provides adequate intake. (5)(69)

Incidence

Early VKDB is rare and is almost exclusively related to maternal medications, especially antiseizure drugs, that increase the degradation of vitamin K (ICH occurs in 20%–25% of such infants) (71).

Classic VKDB often presents with mild symptoms such as gastrointestinal and umbilicus blood loss and rarely ICH; however, VKDB incidence without vitamin K prophylaxis is estimated to be 0.25% to 1.7%. (72)

Late VKDB incidence in exclusively breastfed infants with no vitamin K prophylaxis is 4.4 of 100,000 to 7.2 of 100,000. Infants with fat malabsorption syndromes (cystic fibrosis, cholestatic jaundice, etc) are especially at risk, and sometimes VKDB is the presenting symptom. (72) Late VKDB often presents with ICH. (73)

Diagnosis

In vitamin K–deficient individuals, uncarboxylated vitamin K–dependent proteins, normally called "proteins induced by vitamin K absence" (PIVKA), are present in the blood and can be measured. PIVKA II, or uncarboxylated prothrombin, is a marker of subclinical vitamin K deficiency and is usually present before the development of abnormal coagulation test results. (68)(73)

A confirmed case of VKDB should fulfill the diagnostic criteria of prothrombin time that is 4 times the control value, and at least 1 of the following:

- Normal or elevated platelet count, normal fibrinogen level, and absent fibrin degradation products
- Normalization of prothrombin time after vitamin K administration
- PIVKA (usually PIVKA II) level greater than that of healthy controls

The prompt diagnosis of late VKDB can have important legal consequences in cases of suspected nonaccidental brain injury. Retinal hemorrhage, a signature of nonaccidental brain injury, was recently documented in 2 confirmed cases of VKDB. PIVKA II has a long half-life and can be of major value in retrospective diagnosis of VKDB even weeks after the event. (73)

Vitamin K Prophylaxis

The AAP recommends that vitamin K be given to all newborns as a single intramuscular (IM) dose of 0.5 to 1 mg. The AAP concludes that additional research is needed regarding the oral administration of vitamin K to prevent late VKDB. (72)

Oral administration of vitamin K for the prevention of VKDB was promoted due to concerns regarding a possible causal association between parenteral vitamin K and childhood cancer, a claim that was subsequently and definitively debunked. Orally administered vitamin K prophylaxis, even with multiple-dose regimens, is associated with a resurgence of late VKDB in several countries. (68)(72)

Some oral regimens have proven efficacy in the prevention of late VKDB and are used in Europe, such as the weekly administration of 1 mg of vitamin K for 12 weeks or 2 mg at weeks 1 and 4. However, oral vitamin K is not effective in the prevention of late VKDB in patients with liver disease or malabsorption. (68) Currently, the Canadian Paediatric Society suggests that oral vitamin K should be given to newborns whose parents decline IM vitamin K as a 2-mg dose at birth and at weeks 1 and 6. (74)

Talking Points for the Clinician when Parents Decline Vitamin K Prophylaxis

After the recent increase of infants presenting with late VKDB, the Centers for Disease Control and Prevention (CDC) conducted an investigation and determined that 28% of the parents for children born at local private birthing centers in Tennessee declined vitamin K prophylaxis. Some reasons for parental refusal include concern about an increased risk of leukemia, concern about the use of a synthetic medication, and the impression that giving medications at birth is neither natural nor necessary for healthy term infants. There was a remarkable lack of awareness among the Tennessee families about the potentially life-threatening nature of late VKDB. (69)

When faced with vitamin K refusal, the clinician should respectfully elicit the parents' concerns and attempt to educate and correct any misinformation. The clinician can discuss the recent cases of late VKDB in Nashville, Tennessee, and point out that in all cases the parents had refused the vitamin K prophylaxis at birth.

There is no expert consensus on whether circumcision should be refused or deferred in infants whose parents refuse vitamin K prophylaxis. When confronted with this request there are many considerations. First, there is no available data on the optimal timing of the procedure. Second, the medical provider and the nursing staff comfort with this decision must be taken into analysis because they have to practically manage the bleeding should it occur.

In contemplating the idea of suggesting oral vitamin K to parents who refused the IM injection, it is important to note that oral vitamin K preparations used in Europe with proven efficacy are not available in the United States. The phytonadione 5-mg tablet is the only oral formulation of vitamin K currently approved by the FDA. However, because giving a tablet to a newborn can be challenging and requires crushing or compounding, the injectable phytonadine (1 mg/0.5 mL) is sometimes given orally. Unlike the European vitamin K preparations, US formulations have not been studied for efficacy. (74)

One can argue that delivery of some vitamin K is better than none, but when parents are offered oral vitamin K they seem to perceive it as equally effective as the IM injection. Some parents may consider the IM route if the oral form is not an option. There is also the ethical aspect of prescribing an unproven formulation for the prevention of a potentially life-threatening disease when a treatment of proven efficacy exists. (74)

Summary

- Thirty-four percent of US children and adolescents used vitamin supplements in the past month, and almost half of those children took a supplement daily. (1) Supplement users were more likely to be Asian, white, or non-Hispanic; to belong to families with higher income and education; to be in good or excellent health; and to have access to health care. (2) (Evidence Quality B)
- Vitamin A deficiency is prevalent, especially in the developing world. In fact, vitamin A deficiency accounts for 1.7% of child mortality. (4) (Evidence Quality B)
- The American Academy of Pediatrics recommends a vitamin A supplement for children 6 months to 2 years old who are hospitalized for measles. (9) (Evidence Quality D)
- The recognition and treatment of vitamin B_{12} deficiency is critical, especially in infants, because with early diagnosis it is a reversible cause of developmental regression and cognitive delay. (13)(14) (Evidence Quality D)
- In the exclusively breastfed infant, the most common cause of B_{12} deficiency is undiagnosed maternal pernicious anemia. Other etiologies include maternal gastric bypass surgery and vegetarian diet. (13) (Evidence Quality D)
- Neurologic symptoms secondary to B_{12} deficiency can occur without hematologic abnormalities. (13) (Evidence Quality D)
- It is reasonable to suspect B_{12} deficiency in any infant with failure to thrive and developmental regression. (14) (Evidence Quality D)
- Symptoms of vitamin C deficiency can develop after 30 to 40 days of consuming a diet that is void of vitamin C. (22) Scurvy should be considered in the differential diagnosis of an at-risk child (especially in the setting of a developmental disorder and a restrictive diet) who presents with refusal to walk. (21)(22) (Evidence Quality D)
- Infants and children aged 0 to 1 year need at least 400 IU/d of vitamin D. Children 1 year and older need at least 600 IU/d of vitamin D. (27) (Evidence Quality A)
- Infants and children aged 0 to 18 years who are vitamin D deficient can be treated with 2,000 IU/d of vitamin D_2 or D_3, or with 50,000 IU of vitamin D_2 or D_3 once a week for 6 weeks to achieve a blood level of 25(OH)D greater than 30 ng/mL (>75 nmol/L). (27) (Evidence Quality B)
- Universal screening of all patients for vitamin D deficiency is not recommended and should be reserved and considered only for high-risk patients. (27) (Evidence Quality D)
- Vitamin E at a dose of 800 IU/d is beneficial for the treatment of nonalcoholic steatohepatitis in adults. More studies are needed before its use can be recommended in children. (55)(56) (Evidence Quality D)
- Since the Food and Drug Administration authorized the addition of folic acid to enriched grain products in 1996 there has been a dramatic decrease in folate deficiency and neural tube defects. (61) (Evidence Quality C)
- Recognition of vitamin K deficiency bleeding (VKDB) is critical for prompt diagnosis and urgent therapy. Warning bleeds (umbilical cord, gastrointestinal, or circumcision bleeding) precede ICH by days to weeks. (70) (Evidence Quality C)
- The American Academy of Pediatrics (AAP) recommends that vitamin K be given to all newborns as a single intramuscular dose of 0.5 to 1.0 mg. The AAP concludes that additional research is needed regarding the oral administration of vitamin K to prevent late VKDB. (72) (Evidence Quality C)

References for this article are at http://pedsinreview.aappublications.org/content/39/4/161.

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1. A 20-month-old boy is brought to the pediatrician's office for a well-child checkup. He has recently immigrated to the United States from East Africa. The mother reports that he has trouble seeing at night and stumbles repeatedly. On physical examination, his cornea is normal. You diagnose the patient as having night blindness. Deficiency of which of the following vitamins is most likely responsible for this condition in this patient?

   A. Vitamin A.
   B. Vitamin B_{12}.
   C. Vitamin C.
   D. Vitamin D.
   E. Vitamin E.

2. You are part of the Global Health Brigade and are taking care of a hospitalized infant with measles in rural Uganda. According to the American Academy of Pediatrics, which of the following is the recommended dose of vitamin A supplementation in this patient?

   A. 10,000 IU.
   B. 50,000 IU.
   C. 100,000 IU.
   D. 200,000 IU.
   E. 300,000 IU.

3. In your office you are seeing a 4-month-old girl for failure to thrive. The child was born at term, and the mother had an uneventful pregnancy. You notice that since the last time you saw her, she has been having some trembling movements and has lost her deep tendon reflexes. The child is exclusively breastfed, and the mother is strictly vegan. You decide to send the patient to the hospital for direct admission. In addition to a complete blood cell count, which of the following vitamin serum levels will you most likely order in this patient?

   A. Vitamin A.
   B. Vitamin B_{12}.
   C. Vitamin C.
   D. Vitamin D.
   E. Vitamin E.

4. You practice in a small clinic in the Northeastern United States and are seeing an African American toddler who does not play outside because of the cold weather. He was exclusively breastfed until 6 months of age. He mostly eats pureed foods and does not like eating any dairy foods. You notice that he walks with bowed legs and has widening of wrists on physical examination. Based on the history and physical examination findings, which of the following is the most likely diagnosis in this patient?

   A. Langerhans cell histiocytosis.
   B. Megaloblastic anemia.
   C. Osteogenesis imperfecta.
   D. Rickets.
   E. Scurvy.

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5. You are a pediatrician practicing in rural Tennessee and are seeing a 6-week-old girl who was born at home. Per the parents, there were no problems at birth, and she has been exclusively breastfed. She has not been previously seen by a medical provider. She now presents with poor feeding, irritability, and a bulging fontanelle. Which of the following is the most likely underlying vitamin deficiency to explain the presumed diagnosis of intracranial hemorrhage?

   A. Hypervitaminosis A.
   B. Hypervitaminosis D.
   C. Vitamin B_6 deficiency.
   D. Vitamin K deficiency.
   E. Vitamin E deficiency.

Atopic Dermatitis

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Education Gap

Clinicians are often challenged in the primary care setting with children who present with moderate-severe recalcitrant atopic dermatitis. Many patients present at the subspecialist level grossly undertreated with topical medications and emollients. Recently, numerous clinical investigations have evolved our understanding of the pathogenesis of atopic dermatitis, and the American Academy of Dermatology released new atopic dermatitis guidelines in 2014. Understanding the groundbreaking discoveries in disease pathogenesis and implementing up-to-date management guidelines in clinical practice are critical for pediatricians.

Objectives

After completing this article, readers should be able to:

1. List the age-specific clinical features of atopic dermatitis (AD).
2. Understand the essential, important, and associated diagnostic criteria of AD.
3. Recognize the atopic and nonatopic clinical comorbidities associated with AD.
4. Understand the cutaneous infectious complications associated with AD.
5. Understand the disease pathogenesis and its relationship to therapeutic management.
6. Understand the state-of-the-art treatment guidelines, including the recent "proactive" maintenance therapy recommendations.
7. Recognize the importance of multidisciplinary management and clinical indications for subspecialty referral.
8. Understand effective strategies of therapeutic patient education and implement them into clinical practice.

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ABBREVIATIONS

AD	atopic dermatitis
ADHD	attention-deficit/hyperactivity disorder
AE	adverse effect
FDA	Food and Drug Administration
FLG	filaggrin
IgE	immunoglobulin E
IL	interleukin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
Th	T helper
WWT	wet wrap therapy

INTRODUCTION

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease with a frequently remitting and relapsing course. It is postulated as the first manifestation of the "atopic march"—often preceding the later development of food allergies, allergic rhinitis, and asthma. The terms *atopic dermatitis* and *eczema* are commonly used interchangeably to describe eczematous dermatitis, although technically there are eczemas other than AD, including allergic contact dermatitis and irritant dermatitis. The cardinal features of AD include xerosis, pruritus, eczematous lesions in the typical morphology and distribution, and a personal or family history of atopy.

The personal, social, emotional, and financial resources of patients, their caregivers, and the health-care system are largely burdened by AD. Not including the lost opportunity costs and productivity, such as missed work or school days, or the loss of individual quality of life, annual US economic burdens are conservatively estimated to be approximately $5 billion. (1) An estimated two-thirds of patients with AD initially present with mild disease and may be managed by their primary medical care provider. (2) Pediatricians are nearly always a child's first line of management, and the purpose of this review is to provide up-to-date information regarding AD pathophysiology, clinical presentation, and state-of-the-art treatment guidelines.

EPIDEMIOLOGY

Atopic dermatitis is the most common chronic inflammatory dermatologic disorder in children, affecting an estimated 12.5% of children in the United States. (3) Sixty percent of children with AD present in the first year after birth, and 90% present by 5 years of age. (3) Numerous studies suggest that AD affects both sexes nearly equally. (4) Most children with AD present with mild disease (67%), and the remaining 33% present with moderate-to-severe AD. (3)

Multiple investigations have analyzed the demographic and geographic associations with AD. A study published in 2011 by Shaw et al (5) using National Survey of Children's Health data reported an increased disease prevalence in individuals of African American race. In addition, higher educational level (greater than high school) is associated with higher rates of AD. (5)(6) Domestically, the regions with highest disease prevalence in the United States include numerous northeastern states as well as Idaho, Nevada, and Utah. (5) The prevalence of AD has risen dramatically during the past 50 years in developed countries, especially in the United States, Europe, and Japan. (6) In addition, the incidence of pediatric AD in developing countries seems to be rising, with a maximum prevalence of nearly 30% in some populations. (7) The causes of the increasing prevalence of pediatric AD are unknown, but several systematic large-scale studies point to numerous genetic and environmental factors as potential contributors. (7)

PATHOGENESIS

A major debate has existed as to whether AD is primarily driven by immune abnormalities (inside-out theory) or epidermal barrier dysfunction (outside-in theory). It is clear that AD pathogenesis is multifactorial, resulting from a complex interplay among epidermal barrier dysfunction, immune dysregulation, and environment. Numerous studies have suggested genetic susceptibilities for AD. (8) Preceding classification of the human genome, concordance in monozygotic twin studies and case reports detailing transfer of AD after bone marrow transplant supported a genetic basis for the disorder. (9) Most recently, groundbreaking research worldwide has positively associated 46 genes with AD. (8) Of these investigations, the most steadily replicated findings involve variations in genes encoding filaggrin (FLG), which is also implicated in the etiology of ichthyosis vulgaris. Ichthyosis vulgaris presents with xerotic skin, especially on the extensor surfaces of the legs, is associated with hyperlinear creases on the palms and feet and is due to homozygous or heterozygous deficiencies in the *FLG* genes.

In the superficial epidermis, FLG influences epidermal differentiation, affects barrier function (preventing water loss and blocking the entry of foreign substances), promotes skin hydration, and modulates immune function. (10) It may be that more porous skin is more easily sensitized by skin contactants. Studies have shown that *FLG* gene mutations are associated with higher rates of AD development, more common in certain populations than others, and that variation in *FLG* gene copy numbers (influencing FLG protein expression) influence the development of AD.

Environmental factors undoubtedly interact with genetic susceptibilities, resulting in the clinical expression of AD. Mechanical injury, allergens, and microbes activate the skin's innate immune system, leading to increased expression of specific cytokines that incite inflammation, notably thymic stromal lipoprotein, interleukin (IL)-25, and IL-33. These cytokines trigger type 2 innate lymphoid cells to activate T helper (Th) 2 cells. Increased Th2 cell activity promotes specific cytokine-associated inflammation, eosinophilia, and immunoglobulin E (IgE) production while suppressing epidermal barrier proteins and antimicrobial peptides (IL-4, IL-5, IL-13). The Th2 response also contributes to pruritus by promoting IL-31 production along with several other mediators, including thymic stromal lipoprotein, histamine, tryptase, and neuropeptides. Interleukin-17, a cytokine implicated in the etiology of psoriasis, is also increased in AD, but this association is poorly understood. In addition, barrier function is markedly impaired due to a decline in expression of the structural proteins and lipids that play a role in water retention and barrier protection. Also of importance, Th1 and Th22 cytokines are significantly increased in chronic AD, in addition to Th2 cytokines. The novel Th22 cytokine IL-22 has recently been linked to lichenification through impairing epidermal differentiation and promoting epidermal hyperplasia. These factors contribute to the acute and chronic clinical presentation of AD. (3)(11)(12)

RISK FACTORS FOR DISEASE DEVELOPMENT

Of the numerous risk factors linked with AD, 2 are greatly associated—*FLG* gene mutations and a family history of atopic disease. More than two-thirds of children with AD have an immediate family member with atopic disease. The chances of developing AD increase exponentially with parental atopy. The risk of developing AD is 2 to 3 times more likely with 1 atopic parent and 3 to 5 times more likely with 2 atopic parents. (13) Furthermore, a robust quantity of literature has acknowledged the association between *FLG* mutations and AD. Sixty percent of individuals with *FLG* mutations ultimately develop AD—more than 3-fold higher than the occurrence in the general population. (10) This association is reinforced by numerous studies showing a positive correlation between *FLG* mutations and severe AD. Further investigations highlighted the higher incidence of eczema herpeticum and asthma in patients with AD with *FLG* mutations (10)(14). Conversely, 40% of children with *FLG* mutations do not develop AD, and these mutations are uncommon in specific populations. A recent genomic study of 100 South African children with severe AD and ichthyosis vulgaris showed no *FLG* mutations in this population, and an analogous study of 75 Ethiopian children revealed an *FLG* mutation incidence of 1.3%, much lower than the 10% prevalence documented in individuals of European ancestry. (15)(16) Loss-of-function mutations are also uncommon in African American individuals. (17)

Other environmental exposures in genetically susceptible children may increase the risk of AD, but this is highly controversial. Two clinical investigations of independent birth cohorts revealed a correlation between cat ownership at birth and the development of AD in individuals with *FLG* loss-of-function mutations. (18)(19) Another investigation suggested that dog ownership from birth may reduce the incidence of AD. (20)

Multiple studies suggest a positive correlation between urban environment and atopic disease prevalence. (21) These findings support the hygiene hypothesis, which speculates that early exposure to pathogens may serve as protective in the development of atopy, and in the absence of such exposure, atopic conditions become more prevalent. Several different rural pathogens have been proposed to safeguard individuals from the development of atopic disease, including farm animals, unpasteurized milk, and helminthes. (22)

CLINICAL FINDINGS

Hallmark clinical findings of AD include xerosis (dry skin), pruritus, and eczematous lesions in an age-specific distribution. Morphologically, erythema, lichenification, crusting, exudation, and excoriation characterize the lesions. Skin involvement varies from mild and localized to severe and widespread. The skin of AD is termed by some to be sensitive, with lower thresholds for irritation and pruritus. Pruritus is the most bothersome symptom to children and caregivers, which often significantly worsens quality of life. The resulting "itch-scratch" cycle is a major root of morbidity leading to complications such as secondary infection and poor sleep quality. Pruritus may be exacerbated by factors such as xerosis, coarse clothing (eg, wool), environmental irritants (temperature extremes, harsh soaps or detergents), and allergens.

Classically, AD lesions are characterized as poorly demarcated eczematous plaques; however, the presentation often varies according to age and race. Three distinct age-associated phases—infantile, childhood, and adult—define the usual distribution of AD lesions. The infantile phase typically evolves in the first few years of life, and the childhood and adult phases are distinguished by the initiation of puberty. Noteworthy, the symptoms of individuals occasionally fall outside their age-specific phase.

Characteristic infantile eczema is typically on the scalp, cheeks, and forehead. Lesions progressively extend to involve the trunk and extensor surfaces of extremities. The diaper region is typically shielded from involvement as a result of protection from transepidermal water loss and external irritation. Flexural surface involvement is common in childhood AD. Most frequently, lesions arise in the antecubital and popliteal fossa. Other well-established sites of involvement include the perioral region, wrists/ankles, and neck. Parents often voice concerns about the pigmentary changes, although these typically resolve without long-term scarring. From puberty forward, major areas of involvement consist of the face (periorbital and perioral regions), dorsal feet, hands, and upper back.

The expressed phenotype of AD may vary according to race. African American children often present with more papular or follicular AD. Furthermore, increased pigmentary changes, both hypopigmentation and hyperpigmentation, may be noted in darker skin–type patients, especially in lichenified or resolving areas. Other classic cutaneous conditions associated with AD include keratosis pilaris, ichthyosis vulgaris, and pityriasis alba. Keratosis pilaris is characterized by follicular hyperkeratosis of the extensor surfaces of the upper arms and legs and the face. These rough-feeling keratotic papules are highly associated with ichthyosis vulgaris, an autosomal dominant disorder defined by generalized xerosis and hyperkeratosis. Pityriasis alba is a common concurrent condition, often presenting with blotchy hypopigmentation of the face. More common in patients with AD, it is thought to be due to the hyperkeratosis of the epidermis, which decreases UV penetration. Pityriasis alba and postinflammatory hypopigmentation may overlap, although pityriasis alba can be seen in individuals without underlying AD. Parents may be reassured that these hypopigmented patches gradually improve with time and sun protection.

CLINICAL COMORBIDITIES

Numerous investigations have supported the relationship between AD and other atopic disorders, including asthma, allergic rhinitis, and food allergies. (23) Noteworthy, patients with AD with *FLG* mutations have an additional risk of developing other atopic disorders, especially asthma and peanut allergy. (24)

Additional associations between AD and nonatopic comorbidities have recently been highlighted in the literature. Sleep disruption is the most prevalent comorbidity, affecting up to 60% of children with AD. (25) Pruritus during AD exacerbations causes increases in sleep disturbance, which may lead to neurocognitive impairment, affecting school performance, peer relations, and familial interactions. (25) Studies have also linked neurobehavioral disorders with AD. Several studies of children with AD found a significantly increased prevalence of concomitant attention-deficit/hyperactivity disorder (ADHD) and additional psychiatric disorders, including anxiety, conduct disorder, and depression. (26)

Finally, emerging evidence for comorbidities, including cancer, hypertension, and obesity, is controversial, requiring further investigation. (27) The prospect of these associated comorbidities highlights the importance of obtaining a complete review of systems when evaluating patients with AD and implementing a multidisciplinary approach in their management.

MAKING THE DIAGNOSIS

The diagnosis of AD is primarily clinical, based on a constellation of essential, important, and associated features listed in Table 1. A task force of AD experts updated diagnostic guidelines at a 2013 consensus conference organized by the American Academy of Dermatology. Essential features in the diagnosis of AD include pruritus, chronic relapsing eczematous dermatitis, and age-specific distribution. Other compelling associations include personal or family history of atopy and IgE reactivity; however, these are not essential for diagnosis. Table 1 lists additional clinical findings that are commonly associated. Finally, a diagnosis of AD is contingent on ruling out a variety of additional conditions, including seborrheic dermatitis, scabies, contact dermatitis, psoriasis, and others, as well as other less common conditions that may present with eczematous-appearing rashes (Table 1). (23)

The severity of AD may be delineated through several methods. Numerous scoring systems have been used for clinical trials, such as the Eczema Area and Severity Index, the Investigator Global Assessment, and the Scoring Atopic Dermatitis, but they are not generally used in clinical practice. Generally, milder disease will involve less body surface area and have skin lesions with less erythema, papules, edema, excoriations, lichenification, and intensity of itch. Disease persistence, frequency of flares, effect on quality of life, and comorbidities may influence severity classification. More severe disease may require more aggressive treatment and consideration for referral to a specialist. (23)

DIFFERENTIAL DIAGNOSIS

Table 2 lists the core differential diagnosis of AD. Less common diagnoses are also listed in Table 2, which should be considered in individuals presenting with atypical rash, poor response to therapy, unusual infections, and/or failure to thrive. This differential diagnosis includes infectious, neoplastic, genetic, immunodeficiency, and inflammatory etiologies. When considering a diagnosis of AD, these clinical disorders must first be excluded. (23)

INFECTIOUS COMPLICATIONS

It is commonly recognized that individuals with AD have a high frequency of infectious complications. This stems largely from the increased occurrence of *Staphylococcus aureus* colonization in the AD population. (28) Recent studies involving patients with AD document *S aureus* colonization in up to 90% of actively affected skin and 76% of nonaffected skin. (29)(30) This sharply contrasts with the 2% to 25% prevalence of colonization in controls. (29)(30) The increased adherence of *S aureus* to superficial skin cells, impaired epidermal barrier function, and insufficient production of antimicrobial peptides promote

TABLE 1. Essential, Important, and Associated Features Used for the Clinical Diagnosis of Atopic Dermatitis

ESSENTIAL FEATURES	IMPORTANT FEATURES	ASSOCIATED FEATURES
Both must be present:	Add support to the diagnosis, observed in most cases of AD:	Suggestive of AD, but too nonspecific to be used for defining or detecting AD in research or epidemiologic studies:
1. Pruritus	1. Early age at onset	1. Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
2. Eczema (acute, subacute, chronic)	2. Atopy	2. Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
A. Typical morphology and age-specific patterns:	A. Personal and/or family history	3. Ocular/periorbital changes
a. Infants/children: facial, neck, and extensor involvement	B. Immunoglobulin E reactivity	4. Other regional findings (eg, perioral changes/periauricular lesions)
b. Any age group: current or previous flexural lesions	3. Xerosis	5. Perifollicular accentuation/lichenification/prurigo lesions
c. Sparing of the groin and axillary regions		
B. Chronic or relapsing history		

AD=atopic dermatitis.

Adapted with permission from Eichenfield LF, Boguniewicz M, Simpson EL, et al. Translating atopic dermatitis management guidelines into practice for primary care providers. Pediatrics. *2015;136(3):554–565.*

colonization and, ultimately, cutaneous and/or systemic infection. (31)(32) The cutaneous manifestations of *S aureus* superinfection are characterized by honey-colored crusting, weeping, and pyoderma. Several case reports document severe systemic complications likely resulting from *S aureus* colonization in patients with AD, including bacteremia, sepsis, endocarditis, and osteomyelitis. (33)(34)

Group A *Streptococcus* also accounts for a significant number of AD superinfections. A retrospective review of children with AD with skin cultures revealed colonization with group A *Streptococcus* in 16%. (35) Furthermore, children with group A *Streptococcus* superinfection had a greater frequency of fever, facial involvement, and hospitalization than patients with staphylococcal etiology. (35)

Patients with AD may have an increased risk of developing disseminated viral infections. Eczema herpeticum may present as umbilicated vesicopustules resulting from herpes simplex virus. The hallmark of this condition is grouped vesicles in a "cluster of grapes" appearance overlying diffuse eczematous papules and plaques. Patients can manifest with severe pruritus, pain, and systemic illness, often requiring hospitalization. Molluscum contagiosum, a common ailment of childhood, tends to be more prevalent and can be more severe in children with AD, in addition to inducing eczematous rashes. Molluscum is characterized as a dome-shaped papule with a central white core and/or umbilication. Recently defined in the literature, eczema coxsackium characterizes the atypical clinical presentation of coxsackie virus (CVA6) in children with AD. Mathes et al (36) first described a vesicular pattern with erosions, morphologically similar to eczema herpeticum, localized to areas previously or currently affected by AD. This published constellation of findings suggests that eczema coxsackium should be considered in the differential diagnosis of patients with AD presenting with vesicular lesions. (36)

MANAGEMENT

Figure 1 summarizes the American Academy of Dermatology recommendations for AD therapeutic management for pediatric providers. These guidelines are further detailed throughout this section.

Basic Management

The cornerstone of successful AD management is the implementation of basic management strategies, including good bathing practices and adequate skin hydration. Individuals with AD have baseline xerosis due to barrier function deficits and an unfavorable balance of transepidermal water loss and water retention. Bathing may hydrate skin

TABLE 2. **Core Differential Diagnosis and Less Common Diagnoses of Atopic Dermatitis**

CORE DIFFERENTIAL DIAGNOSIS
• Scabies
• Psoriasis
• Ichthyoses
• Seborrheic dermatitis
• Contact dermatitis (irritant or allergic)
• Cutaneous T-cell lymphoma
• Photosensitivity dermatoses
• Immunodeficiency diseases
• Erythroderma of other causes

OTHER DIAGNOSES TO CONSIDER

Nutritional and Metabolic Disorders	Primary Immunodeficiency Disorders	Other Disorders
• Acrodermatitis enteropathica	• Agammaglobulinemia	• Ataxia-telangiectasia
• Biotin deficiency	• Hyperimmunoglobulin E syndrome	• Langerhans cell histiocytosis
• Celiac disease • Essential fatty acid deficiency • Hartnup disease • Hurler syndrome • Phenylketonuria • Prolidase deficiency • Zinc deficiency	• Omenn syndrome • Severe combined immunodeficiency disorder • Wiskott-Aldrich syndrome	• Netherton syndrome

and reduce irritants, bacteria, and crusts. Expert consensus recommends bathing in lukewarm water followed by application of moisturizer or topical prescription medications. The use of mild or nonsoap cleansers is preferred to avoid irritation and detrimental barrier effects. Transepidermal water loss may result from water evaporation after bathing if moisturizer is not applied. Thus, application of emollients after bathing is encouraged to retard evaporation of water. Applying emollients generously at least twice daily is additionally recommended to boost cutaneous hydration and provide symptomatic relief. (37) Emollient choice is highly dependent on provider and patient predilection. Thicker occlusive agents, such as ointments, may be more effective, but moisturizers vary in formulation and water content and can include ointments, creams, oils, gels, and lotions. Recently, several studies documented anti-inflammatory benefits and enhanced efficacy of emollients with physiologic concentrations of lipids and ceramides. (38)(39)(40) These formulations are more expensive, and the cost-benefit ratio is yet to be established. A variety of studies exploring the efficacy and microbiome effects of specific oils have emphasized that oils are not substitutable. Coconut oil was superior to olive oil in several head-to-head studies in decreasing *S aureus* colonization and AD severity. (41)(42)

Acute Treatment of Exacerbations

Topical corticosteroids (TCSs) have long been established as the first-line therapy for acute flares due to their remarkable anti-inflammatory properties. During the past 60 years, efficacy has been demonstrated in more than 100 clinical investigations. (37) Topical corticosteroids are formulated in a variety of strengths, ranging from lowest potency (group VII) to highest potency (group I). Examples of alternatives in each class are shown in Table 3. Often, TCSs are prescribed

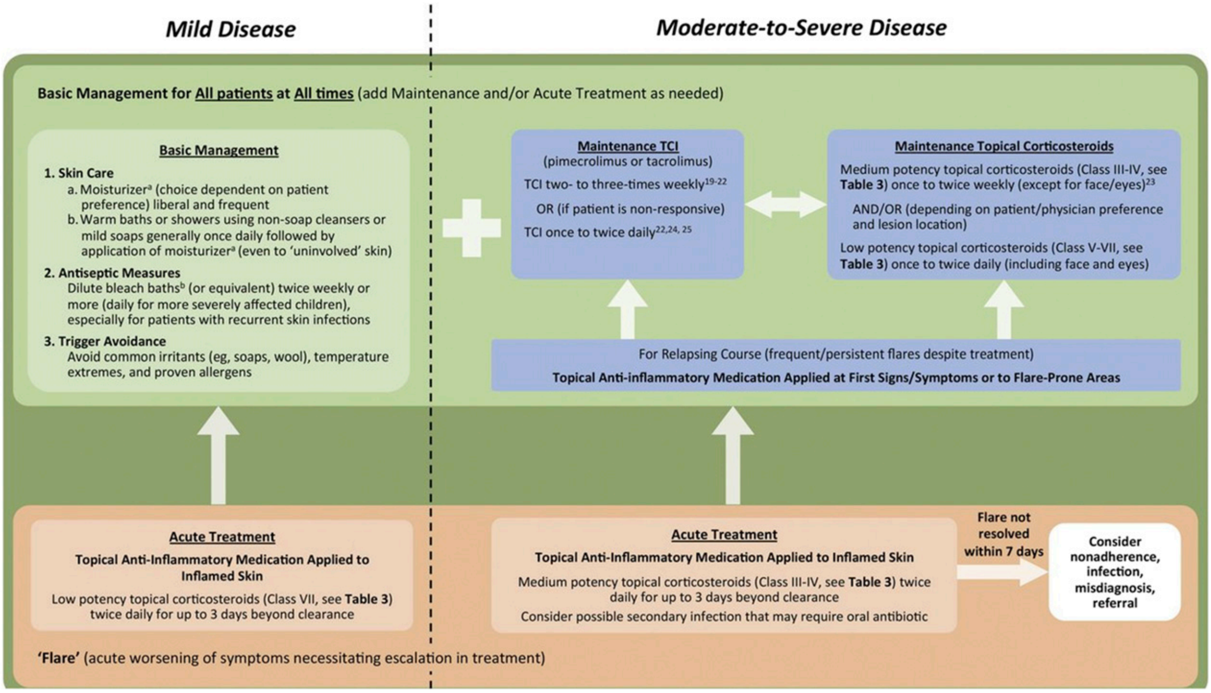

Mild Disease
Moderate-to-Severe Disease
Basic Management for All patients at All times (add Maintenance and/or Acute Treatment as needed)
Basic Management
1. Skin Care
a. Moisturizer^a (choice dependent on patient preference) liberal and frequent
b. Warm baths or showers using non-soap cleansers or mild soaps generally once daily followed by application of moisturizer^a (even to 'uninvolved' skin)
2. Antiseptic Measures
Dilute bleach baths^b (or equivalent) twice weekly or more (daily for more severely affected children), especially for patients with recurrent skin infections
3. Trigger Avoidance
Avoid common irritants (eg, soaps, wool), temperature extremes, and proven allergens
Maintenance TCI
(pimecrolimus or tacrolimus)
TCI two- to three-times weekly19-22
OR (if patient is non-responsive)
TCI once to twice daily22,24, 25
Maintenance Topical Corticosteroids
Medium potency topical corticosteroids (Class III-IV, see Table 3) once to twice weekly (except for face/eyes)23
AND/OR (depending on patient/physician preference and lesion location)
Low potency topical corticosteroids (Class V-VII, see Table 3) once to twice daily (including face and eyes)
For Relapsing Course (frequent/persistent flares despite treatment)
Topical Anti-inflammatory Medication Applied at First Signs/Symptoms or to Flare-Prone Areas
Acute Treatment
Topical Anti-Inflammatory Medication Applied to Inflamed Skin
Low potency topical corticosteroids (Class VII, see Table 3) twice daily for up to 3 days beyond clearance
Acute Treatment
Topical Anti-Inflammatory Medication Applied to Inflamed Skin
Medium potency topical corticosteroids (Class III-IV, see Table 3) twice daily for up to 3 days beyond clearance
Consider possible secondary infection that may require oral antibiotic
Flare not resolved within 7 days
Consider nonadherence, infection, misdiagnosis, referral
'Flare' (acute worsening of symptoms necessitating escalation in treatment)

Figure 1. Proposed treatment model/eczema action plan for pediatricians and other primary care providers. (2) TCI=topical calcineurin inhibitor. [a]As tolerated during flare; direct use of moisturizers on inflamed skin may be poorly tolerated; however, bland petrolatum is often tolerated when skin is inflamed. Note: Topical phosphodiesterase-4s were not approved at the time of algorithm development. (Reprinted with permission from Eichenfield LF, Boguniewicz M, Simpson EL, et al. Translating atopic dermatitis management guidelines into practice for primary care providers. *Pediatrics*. 2015;136 (3):558.)

for varying durations of a few days to several weeks to manage AD refractory to basic good skin care and emollient use alone. Low-potency (ie, 1%–2.5% hydrocortisone) and medium-potency (ie, 0.1% triamcinolone) TCSs are recommended as first-line management for flares of mild and moderate-to-severe AD, respectively, especially in infants and young children. (37) Facial and intertriginous areas are very penetrable and should be treated with low-potency corticosteroids to avoid adverse reactions. Recommendations for TCS therapy duration are numerous and largely based on expert consensus. Recently published guidelines for primary care providers endorse continued application of TCS twice daily for up to 3 days beyond flare resolution, (43) but there are data to support sufficient therapeutic response with once daily application. (44) Adequate quantities of mild- to moderate-strength TCS should be described proportionate to age and body surface area involvement. For instance, acute treatment of a 4-year-old with 50% body surface area involvement with a topical corticosteroid ointment applied twice daily should use 62 to 125 g of TCS per week based on "fingertip unit dosing." (45) Patient noncompliance, cutaneous superinfection, and/or misdiagnosis must be considered if the exacerbation fails to improve within 10 to 14 days of therapy. Referral to a dermatologic specialist is recommended for unresponsive dermatitis with appropriate medication use. (43)

To enhance TCS therapy efficacy, wet wrap therapy (WWT) is often used in the management of refractory moderate-severe AD. (46) Health-care providers in the clinical setting may demonstrate this technique to patients with AD and caregivers. The WWT involves the application of TCSs or emollients followed by 2 successive layers of cotton pajamas, gauze, or tubular bandages (first layer wetted with warm water; second layer dry). The occlusive properties of WWT enhance penetration of the topical agent(s), improving treatment success. (46) Wet wrap application for up to 24 hours is acceptable and may be repeated for several days to 2 weeks, permitting patient tolerance. Cautious use of mid-higher potency TCSs in WWT is advised because greater absorption may cause adverse effects (AEs) and/or infection. The WWT should be performed as directed by a practitioner trained in its use. (47)

Rarely, AD worsened by TCSs or other topical therapy may result from allergic sensitization to specific components in topical formulations, including preservatives, vehicle, or active ingredients. (48) Specialist referral for patch testing is recommended if contact dermatitis is suspected. (43)

TABLE 3. Topical Corticosteroids Ranked by Potency (from Most Potent to Least Potent)

GROUP	GENERIC NAME (BRAND NAME)	VEHICLE	CONCENTRATION, %
I	• Betamethasone dipropionate (Diprolene)	Ointment	0.05
	• Clobetasol proprionate (Temovate)	Cream, ointment, lotion	0.05
	• Diflorasone diacetate (Psorcon)	Ointment	0.05
	• Halobetasol propionate (Ultravate)	Cream, ointment	0.05
II	• Amcinonide (Cyclocort)	Ointment	0.1
	• Betamethasone diproprionate (Diprosone/Maxivate)	Ointment	0.05
	• Desoximetasone (Topicort)	Cream, ointment	0.25
		Gel	0.5
	• Fluocinonide (Lidex)	Cream, ointment, gel, solution	0.05
	• Mometasone furoate (Elocon)	Ointment	0.1
	• Triamcinolone (Aristocort)	Cream	0.5
III	• Amcinonide (Cyclocort)	Cream, lotion	0.1
	• Betamethasone diproprionate (Diprosone)	Cream	0.05
	• Betamethasone valerate (Valisone)	Ointment	0.1
	• Diflorasone diacetate (Psorcon)	Cream	0.05
	• Fluticasone propionate (Cultivate)	Ointment	0.005
	• Triamcinolone acetonide (Aristocort)	Ointment	0.1
IV	• Flucinolone acetonide (Synalar)	Ointment	0.025
	• Hydrocortisone valerate (Westcort)	Ointment	0.2
	• Mometasone fuorate (Elecon)	Cream, lotion	0.1
	• Triamcinolone acetonide (Kenalog, Aristocort)	Cream	0.1
V	• Betamethasone dipropionate	Lotion	0.05
	• Betamethasone valerate (Valisone)	Cream	0.1
	• Fluticasone acetonide (Synalar)	Cream	0.025
	• Fluticasone propionate (Cutivate)	Cream	0.05
	• Hydrocortisone butyrate (Locoid)	Cream, ointment, lotion	0.2
	• Hydrocortisone valerate (Westcor)	Cream	0.2
	• Prednicarbate (Dermatop)	Cream	0.1
VI	• Alclometasone dipropionate (Aclovate)	Cream, ointment	0.05
	• Betamethasone valerare	Lotion	0.1
	• Desonide (DesOwen/Tridesilon)	Cream, ointment	0.05
	• Fluocinolone acetonide		
	(Derma-Smoothe/FS)	Oil	0.01
	(Synalar)	Solution	0.01
	• Triamcinolone acetonide (Aristocort, Kenalog)	Cream	0.025
VII	• Hydrocortisone acetate	Cream	1
	• Methylprednisolone acetate	Cream	0.25
	• Dexamethasone sodium phosphate	Cream	0.05

Adapted with permission from Eichenfield LF, Boguniewicz M, Simpson EL, et al. Translating atopic dermatitis management guidelines into practice for primary care providers. Pediatrics. *2015;136(3):554–565.*

The AEs reported from TCS utilization are infrequent and primarily cutaneous, but disproportionate fears of their use are many, with corticosteroid phobia being common. Much "recalcitrant" AD is due to insufficient use of prescribed topical therapy. Therapy noncompliance may result from parental fear of AEs. The true frequency of AEs is unknown, but they are rare in studies and clinical practice. Counseling patients and caregivers on clinical signs and reversibility of AEs, including skin atrophy, telangiectasias, acneiform lesions, and hypertrichosis, is critical to treatment adherence. Systemic AE incidence is extremely rare but increases with prolonged duration of therapy. Rare reports of hypothalamic-pituitary axis suppression, hyperglycemia, and hypertension are documented in the literature. (49) Predisposing factors to systemic AEs include long-term utilization, large body surface area, and high-potency formulation. Providers should be aware of TCS AEs and monitor for associated clinical signs. Specific laboratory monitoring for systemic AEs is not routinely suggested. (37) Pediatricians should feel comfortable prescribing specific quantities of TCS to be used over time, counseling about safe TCS use rather than fueling inappropriate corticosteroid phobia that may contribute to inadequate disease control.

The topical calcineurin inhibitors (TCIs) 0.1% pimecrolimus cream and 0.03% tacrolimus ointment are Food and Drug Administration (FDA) approved for children older than 2 and 15 years, respectively. These topical medications are indicated as "second line therapy for the short term and noncontinuous chronic treatment of moderate to severe atopic dermatitis in nonimmunocompromised children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis or when those treatments are not advisable." (50)

Contrasting with TCS therapy, TCI therapy has fewer cutaneous risks and may be more suitable for thin-skinned areas, such as the face and intertriginous regions. Caregivers and providers often have concerns about TCI treatment in light of the FDA-issued black box warning in 2006. (50) A lack of long-term safety data at the time and concerns of hypothetical risk of skin malignancy and lymphoma led to the issuance of this warning. Since that time, numerous studies involving more than 17,000 infants and children have displayed drug safety with minimal evidence of immunocompromise or malignancies with their use. (51)

Recently, topical phosphodiesterase-4 inhibitors have been studied, and crisaborole 2% topical ointment is FDA approved for AD in children 2 years and older. A nonsteroidal anti-inflammatory agent, it is not associated with skin atrophy. Although it may be incorporated into regimens of care similar to other topical anti-inflammatory medications, it was studied as monotherapy in mild-to-moderate AD applied 2 times a day for 28 days. (52)

"Proactive" Maintenance Therapy

After resolution of disease flare, maintenance therapy largely depends on AD persistence and severity. Control with basic management is typically sufficient for patients with mild disease that is intermittent. Basic management principles include appropriate skin care (detailed previously herein) and irritant avoidance. Emollients constitute an integral part of maintenance and preventive therapy given their cost-effectiveness and capacity to enhance skin hydration. Noteworthy, a recent randomized controlled trial of 124 neonates at risk for atopic disease suggested an inverse correlation between emollient application from birth and subsequent AD development by 6 months of age. (53) Larger-scale investigations are necessary to confirm these encouraging results.

Multiple specialty group guidelines have recommended the use of TCIs and TCSs in proactive maintenance regimens of care. A proactive approach for maintenance therapy is advised to use regularly scheduled topical application of anti-inflammatory medications to frequently flaring skin areas, as contrasted to reactive flare management. Both TCSs and TCIs may be useful on disease-prone areas, applied on a routine periodic basis. Multiple clinical investigations reveal significant flare reduction with proactive consistent application of moderate or lower-potency TCSs, and/or TCIs, with varying application frequencies. (51)(54) Current recommendations allow flexibility, endorsing TCI application 2 to 3 times weekly, or once to twice daily in recalcitrant cases. (55) Similarly, TCSs are recommended once to twice weekly (medium potency; excluding face and intertriginous regions) and/or once to twice daily (low potency; including face and intertriginous regions). (55)

OTHER THERAPEUTIC CONSIDERATIONS

Irritants, Allergy, and Environmental Modifications

Irritants include chemicals, course fabrics (ie, wool), lanolin, soaps/detergents, fragrances, acidic foods, tobacco smoke, and temperature extremes. Avoidance of irritants and known allergens may lessen disease severity and lead to more disease-free days.

Children with AD have higher rates of IgE sensitization, which may be evaluated through specific IgE or skin prick testing. However, IgE sensitization is not the same as clinical food allergy, which is defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." (56) The incidence of IgE-mediated food allergy development in 2 large US-based investigations of infants with mild-to-moderate AD, 1 retrospective and 1 prospective, was approximately 15%. (57) Food allergy rates increased to approximately 30% to 40% in patients with moderate-to-severe disease. (57) The most common food allergens in patients with AD include egg, milk, peanut, soy, and wheat. Food allergens may be a more significant issue in younger children with AD. However, both skin prick and specific IgE tests have high false-positive rates and are not necessarily predictive of clinically relevant reactions. (56)

Food allergy reactions in patients with AD can include elicitation of eczematous changes or urticarial skin findings or systemic symptoms such as wheezing, vomiting, diarrhea, and/or proctocolitis. Suspected food allergy may need to be evaluated with oral food challenges. It is not recommended for children without documented or proven food allergy to avoid potentially allergenic foods as a means of managing AD. An expert panel recommended that children younger than 5 years with moderate-severe AD should undergo food allergy testing if "1) the child has persistent atopic dermatitis in spite of optimized management and topical therapy; and/or 2) the child has reliable history of an immediate reaction after ingesting specific foods." (56) If they do have documented food allergy and AD it is reasonable to avoid the specific food allergens. Regular growth monitoring and nutritional management may be an important part of intervention.

Recently, young children with AD have been identified as a group that may benefit from the early introduction of specific foods, decreasing subsequent development of food allergy. The novel "Learning Early about Peanut Allergy" (LEAP) trial, published in 2015, was the first large-scale randomized trial investigating allergy prevention by early allergen introduction. Children with severe eczema and/or egg allergy were shown to have a decreased rate of development of peanut allergy with early peanut consumption, beginning at 4 to 11 months of age and continuing until 5 years of age. (57) Prevention was shown in children with negative skin prick test results for peanut, as well as those with positive skin prick test results, although individuals with larger wheal size (5 mm) were excluded from the trial. Expert recommendations are advising the identification of children with severe AD in the first year of life as a cohort that should be evaluated with specific IgE to peanut, with early feeding with a negative serum test result and referral to allergy for skin prick testing for positive specific IgE peanut blood test results, or direct referral before serum screening, for skin prick evaluation for determination of the safety of early peanut feeding. (58)(59)

Reactivity to aeroallergens predominates over food allergen sensitization in older children and adolescents with AD. Sensitization to aeroallergens occurs more frequently in patients with moderate-to-severe AD. Common aeroallergens include animal dander, dust mites, fungi, and pollen. Similar to food allergen sensitization, clinical relevance of aeroallergen sensitization is variable, worsening eczema severity in some individuals but not others. Eczematous dermatitis predominantly on exposed cutaneous surfaces, including the arms, face, neck, and V area of the chest, may be a clue to aeroallergen involvement. Avoidance of aeroallergens through environmental modifications has not consistently decreased cutaneous involvement. Numerous investigations have focused on minimizing house dust mite exposure to improve AD severity. Although cleaning measures and mattress covers may reduce house dust mite sensitization, investigations, although few, have shown clinical improvement in patients with AD who undergo these interventions. Current American Academy of Dermatology guidelines advise that pillow and mattress covers may be considered in children with house dust mite sensitization and refractory AD, on the basis of limited evidence. (55)

Microbial Management

Antimicrobial therapy should be reserved for the management of patients with clinical signs of infection. Localized impetigo may be treated topically with antistaphylococcal antibiotics (ie, mupirocin), whereas widespread involvement often requires more aggressive therapy with systemic antibiotics. First-generation cephalosporins provide broad antibacterial coverage against staphylococcal and streptococcal agents except methicillin-resistant *S aureus*. Poor clinical response should prompt culture of affected skin to assess for methicillin-resistant *S aureus* and to guide antibiotic selection based on sensitivity and resistance patterns. Topical or systemic antibiotic treatment of AD that is not clinically infected is not advised. (60)

Hospitalization and intravenous antimicrobials are occasionally required for extensive infections, especially eczema herpeticum. Once a dermatologic emergency, mortality from this potentially lethal condition is virtually prevented with prompt intravenous systemic acyclovir administration. A multicenter retrospective cohort study recently showed an inverse correlation between hospital length of stay and delay in acyclovir initiation, providing further evidence for the efficacy of therapy. (61) Outpatient oral antiviral management is often sufficient for localized outbreaks and should be considered in mild cases.

In children prone to cutaneous bacterial infections, proactive antiseptic bleach baths may reduce AD severity by decreasing inflammation and cutaneous microbial colonization. (62) One randomized placebo-controlled investigation revealed a significant decrease in eczema severity in children 6 to 17 years of age with clinical signs of bacterial infection who received daily 0.005% sodium hypochlorite (bleach) baths for 3 months. (29) The American Academy of Dermatology currently recommends bleach baths (0.005% sodium hypochlorite) twice weekly to daily in patients prone to bacterial superinfections on the basis of this evidence. Instructions for appropriately mixing a therapeutic bleach bath are listed in Table 4.

Pruritus and Sleep Disturbance

The use of topical antihistamines for the symptomatic relief of pruritus in patients with AD is not recommended due to the risk of cutaneous absorption. (37) Short-term treatment with sedating systemic antihistamines is often used to improve sleep quality during flares, although the evidence supporting this is limited. The first-generation antihistamines (ie, diphenhydramine and hydroxyzine) with sedative properties are favorable. Nonsedating antihistamines are not suggested in the absence of other atopic disorders but may be useful for concurrent atopic conditions (ie, allergic rhinitis). (60)

REFRACTORY THERAPEUTICS

Immunosuppressive agents or narrow-band UV-B phototherapy is frequently used at the specialist level for moderate-severe refractory AD that is persistent or frequently flaring despite the use of topical medications. UV radiation is postulated to have immunosuppressive, antibacterial, and barrier-enhancing properties beneficial in AD management. (63) Systemic immunomodulatory agents (ie, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) are sparingly recommended for children recalcitrant to first-line therapies and/or phototherapy. (60) Oral corticosteroids are occasionally used for severe AD flares but are not recommended due to only transient effects and a poor AE profile. Newly established understanding of the immunologic dynamics underlying AD has triggered recent investigations into novel therapeutics, including biological agents and small molecules (eg, IL-4 receptor alpha antibodies (dupilumab), JAK inhibitors, and others. Initial results are encouraging, and further investigations are currently underway.

TABLE 4. Bleach Bath Instructions for Caregivers

1. Add common 6% household bleach to a bathtub full of water (8.75% bleach is one-third more concentrated; use one-third more water or one-third less bleach)
2. Measure the amount of bleach before adding it to the bathwater
3. For a full tub of water, use ½ cup; for a half-full tub of water, add ¼ cup of bleach
4. While the tub is filling, pour the bleach into the water
5. Wait until the bath is fully drawn before placing the child in the tub
6. Never apply bleach directly on a child's skin
7. Soak for 10 min
8. Pat the child's skin dry after the bath
9. If the child uses eczema medication, apply it immediately after the bath, then moisturize the child's skin
10. As an alternative to bleach baths, comparable dilute bleach solutions can be made using 1 tsp of bleach per gallon of water. This may be useful in spray bottles for use in showers (eg, for adolescents) or for smaller baby bathtubs. Alternatively, commercial sodium hypochlorite products that seem to have similar effects as bleach baths are available.

THERAPEUTIC PATIENT EDUCATION

Educating caregivers and patients on disease course, prognosis, and effective implementation of therapeutic interventions is critical to AD management success. Comprehensive education may improve treatment compliance and minimize caregiver misunderstandings and reservations. Teaching should begin with implementation of an initial management plan and continue through each subsequent visit, ensuring continued patient understanding as therapy is continued and/or adapted. Educational methods vary significantly and can be conveyed individually or through group sessions. Numerous different educational interventions have been investigated during the past decade. Evidence strongly supports intensive formal training programs, showing significant improvements in patient disease severity and quality of life. These interventions are often less feasible in clinical practice due to substantial physician and personnel time constraints. (64) Other more practicable educational strategies include written action plans, PowerPoint or video instruction modules, and nurse instructional sessions.

Written action plans have been successful in improving treatment compliance in asthmatic and diabetic children. (64) Numerous clinical providers have used an analogous action plan for patients with AD detailing proper skin care and specific indications for systemic and topical medications. (64) Further studies must be performed on their educational effectiveness, but these written action plans are promising. (64)(65)

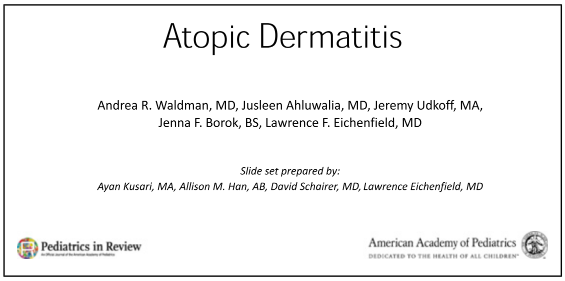
Physicians should be cognizant of additional management resources for patients with AD, including information provided by the American Academy of Dermatology (http://www.aad.org), the National Eczema Association (http://nationaleczema.org), and The Eczema Center at UCSD/Rady Children's Hospital, San Diego (http://www.eczemacenter.org).

Summary

- On the basis of recent epidemiologic evidence, atopic dermatitis (AD) is the most common chronic inflammatory dermatologic disorder, affecting approximately 12.5% of children in the United States (60% by age 1 year and 90% by age 5 years).
- On the basis of recent epidemiologic evidence, disease prevalence is highest in African American children and increases in direct association with parental educational level.
- On the basis of strong evidence, loss-of-function mutations in the *FLG* gene and familial atopy increase the genetic susceptibility to AD development.

- On the basis of expert consensus, AD may be diagnosed clinically based on a constellation of essential, important, and associated features (Table 1).
- On the basis of expert consensus and some research evidence, physicians should be conscious of and evaluate for AD comorbidities, including allergic rhinitis, asthma, food allergies, sleep disturbance, attention-deficit/hyperactivity disorder, anxiety, and depression.
- On the basis of strong evidence, individuals with AD have baseline xerosis for which emollient use is a critical component of management.
- On the basis of some evidence and expert consensus, bathing in lukewarm water for a limited duration using a mild or nonsoap cleanser is recommended to hydrate skin and eliminate residual irritants, bacteria, and crusting.
- On the basis of strong evidence, lowest- to moderate-potency topical corticosteroid (TCS) application for up to 3 days beyond flare resolution is recommended.
- On the basis of some evidence and expert consensus, wet wrap therapy enhances the penetration of topical agents, improving treatment success.
- On the basis of some evidence and expert consensus, antiseptic 0.005% bleach baths may help AD in those with frequent infection.
- On the basis of strong evidence, "proactive" maintenance therapy with TCSs once or twice weekly or topical calcineurin inhibitors (TCIs) twice weekly to daily is efficacious in decreasing flare frequency.
- On the basis of strong evidence, TCIs may be safely used off label in children younger than 2 years.
- On the basis of some evidence and expert consensus, educating caregivers and patients on disease course, prognosis, and effective implementation of therapeutic interventions is critical to AD management success.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/4/180.supplemental.



Atopic Dermatitis

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1. A 10-month-old girl is brought to you for evaluation of a skin rash. Both parents have a history of eczema. On physical examination, her skin is dry, with poorly demarcated plaques. Given this child's age, the presence of plaques over which of the following locations of her body is most likely consistent with eczematous plaques?
   - A. Diaper region.
   - B. Dorsum of the feet.
   - C. Flexural skin surfaces.
   - D. Scalp, cheeks, and forehead.
   - E. Upper back.
2. A 5-year-old boy has a history of eczema since infancy. He has been treated with daily emollients and intermittent topical corticosteroids with good response. He is now in kindergarten, and he is brought to you by his parents for evaluation of honey-colored crusted lesions in the antecubital skin regions bilaterally with similar lesions in the popliteal fossae. He has had no fever. You are concerned that his skin lesions are infected. Which of the following pathogens is the most likely cause of the skin infection in this patient?
   - A. Coxsackie virus.
   - B. Group A *Streptococcus.*
   - C. Herpes simplex virus.
   - D. *Staphylococcus aureus.*
   - E. *Staphylococcus epidermidis.*
3. A 7-year-old girl has had eczema treated with increasing strength of topical corticosteroids. On a routine physical examination she is found to have eczematous plaques on the flexural surfaces of her wrists, elbows, and knees. You are concerned that she is not responding to increasing strength of prescribed therapies. Which of the following is the most likely etiology of poor response to therapy that must be considered first in this patient?
   - A. Allergy to emollient therapy.
   - B. Bacterial infection of skin lesions.
   - C. Hypothalamic-pituitary axis suppression.
   - D. Missed diagnosis of pityriasis alba.
   - E. Noncompliance due to parental fear of corticosteroid adverse effects.
4. A 4-month-old boy is brought to you for a health supervision visit. Family history is strongly positive for atopy. He has 2 older siblings who have eczema, and 1 of his siblings has asthma. There is also a strong family history of food allergies that include allergies to nuts, eggs, corn, and wheat. The family would like to discuss the introduction of foods into their son's diet over the next few months. Which of the following is the most appropriate recommendation to give regarding solid food introduction in this patient?
   - A. Avoidance of all bread products.
   - B. Avoidance of eggs until 2 years of age.
   - C. Early introduction of peanut.
   - D. Prolonged rice-based diet.
   - E. Soy-based diet until 3 years of age.

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5. You care for a 12-year-old girl who has been hospitalized several times with bacterial skin infections related to her atopic dermatitis. She and her family are well-educated regarding the use of emollients and topical corticosteroids, but she continues to have recurrent bacterial skin infections. To decrease the frequency of skin superinfections, which of the following is the most appropriate preventive measure to recommend for this patient?
    A. Daily 0.005% sodium hypochlorite (bleach) baths for 3 months.
    B. Intramuscular ceftriaxone 100 mg/kg monthly for 3 months.
    C. Intravenous solumedrol 2 mg/kg infusion.
    D. Oral prednisone 1 mg/kg corticosteroid burst for 1 week.
    E. Oral cephalexin 50 mg/kg for 1 month.

Clinical Presentation, Evaluation, and Management of Neuroblastoma

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Education Gap

Pediatricians play a pivotal role in the diagnosis of neuroblastoma and as such should be aware of the elusive signs and symptoms to provide clinical surveillance, appropriate referral, and medical support as part of the patient's multidisciplinary team.

Objectives After completing this article, readers should be able to:

1. Identify signs and symptoms of neuroblastoma.
2. Identify patients who require emergency care for a life-threatening presentation.
3. Discuss the basics of clinical presentation, diagnostics, and management of neuroblastoma.

INTRODUCTION

Pediatric cancers occur in 171 per 1 million children in the United States each year and are the leading cause of disease-associated death in children. (1) Neuroblastoma is not only the most common cancer in infancy but also the most prevalent solid tumor outside the cranium, (2) and it sometimes requires the most aggressive treatment plan in pediatric oncology. Therefore, pediatricians should be familiar with clinical presentations that should prompt appropriate and timely referral. In this review, we present neuroblastoma, which exemplifies several principles of pediatric oncology, including its multidisciplinary treatment approach.

EPIDEMIOLOGY

The annual incidence of neuroblastoma is approximately 700 cases in North America. (1) In a review of national cancer registries from 2001 through 2009, a diagnosis of neuroblastoma or ganglioneuroblastoma was found in approximately 6% of the cases. (1) Neuroblastoma is more common in the white population (9.7 per 1 million) than in the African American population (6.8 per 1 million) (2) and more common in males (8.5 per 1 million) than in females (7.6 per 1 million).

AUTHOR DISCLOSURE Drs Sharma, Mer, Lion, and Vik have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CBC	complete blood cell
CT	computed tomography
HVA	homovanillic acid
IHC	immunohistochemical
IL-2	interleukin-2
mIBG I-123	metaiodobenzylguanidine
MRI	magnetic resonance imaging
OMS	opsoclonus myoclonus syndrome
VMA	vanillylmandelic acid
WBC	white blood cell

(3) Although the median age at diagnosis of neuroblastoma is 18 months, (4) there is a wide age range, from in utero diagnosis to individuals in their 20s. (5) Research studies have interrogated several exposures, including viruses, chemicals, radiation, and drugs. No strong causality has been found to support a role of environmental risk factors in the pathogenesis of neuroblastoma.

PATHOPHYSIOLOGY

Neuroblastoma arises from abnormal growth of embryonic neural crest cells that normally make up the sympathetic ganglia and the adrenal medulla. (6) As in all cancers, this aberrant growth is caused by gene mutations. Serving as a starting point, the gene mutation may be germline (occurring in sperm or eggs, thereby hereditable) or somatic (in other cells of the body, which become a tumor).

In some cases, hereditable gene mutations predispose to neuroblastoma. A germline mutation in the *ALK* oncogene accounts for less than 2% of all neuroblastoma cases and is known as familial neuroblastoma. Familial neuroblastoma often presents with severe clinical features, such as younger age at diagnosis, bilateral adrenal tumors, and multifocal primary neuroblastoma. (7) A *PHOX2B* loss-of-function mutation can result in neuroblastoma as one feature of congenital central hypoventilation syndrome. (8)(9) A neurocristopathy syndrome is a rare, heritable group of conditions that result from abnormal neural crest cell development and must be considered when seeing a child with simultaneous occurrence of Hirschsprung disease, congenital hypoventilation syndrome, and congenital neuroblastoma.

In contrast, somatic mutations account for more than 98% of neuroblastoma cases. (10) Several genetic alterations have been identified, including gene amplification, chromosomal alterations, and gene polymorphisms. The most important biomarker in neuroblastomas, the *MYCN* gene, is amplified in approximately 20% of cases. (11) The *ALK* oncogene has also been shown to have gain-of-function somatic mutation in approximately 14% of neuroblastomas. (12) Both *MYCN* and *ALK* amplifications are associated with aggressive tumor phenotype and poor prognosis. Recurrent gain or loss of specific chromosomal segments is found in almost all high-risk neuroblastomas. The most important alterations include gain of 17q and loss of 11q and 1p. (6) Ongoing research efforts are underway to better understand genes that are housed in the aforementioned chromosomal regions, which are associated with aggressive neuroblastomas. Finally, the number of whole chromosomes in a cell, also known as ploidy, is another prognostic marker. Tumor cells can have more (hyperploidy) or less (hypoploidy) than the normal number of copies of whole chromosomes. As with neuroblastomas and most other pediatric cancers, hyperploidy is a more favorable prognostic sign than hypoploidy. (13) Conclusively, there is a great variety of genetic alterations possible, leading to a wide spectrum of clinical behavior of neuroblastomas. The following cases show the dramatic extremes of presentation.

CLINICAL PRESENTATION

Case 1

Katie is a 4-month-old healthy girl who is brought to her pediatrician by her mother with a concern of "projectile vomiting" for 3 days. Katie's mother is worried that she may have pyloric stenosis just as her older brother did when he was an infant. The mother denies sick contacts. Urinary output has been adequate, and Katie is gaining weight adequately. Katie's vital signs and physical examination findings are normal. A complete abdominal ultrasound is negative for pyloric stenosis. However, it is positive for an incidental finding of a 2-cm heterogeneous mass in the right retroperitoneal space. The mass may be arising from the adrenal gland, and it contains areas of calcification, with partial vascularity on Doppler, and is not causing mass effect. On consultation, a pediatric oncologist would like to see Katie in her clinic today, with plans to obtain a complete blood cell (CBC) count, basic metabolic panel, liver enzyme levels, coagulation profile, and random urinary catecholamine levels.

This case demonstrates 1 side of the clinical spectrum, in which a neuroblastoma may be discovered as an incidental radiologic finding. The symptoms, which brought her to the pediatrician, may very well be unrelated to the neuroblastoma. In addition, a small neuroblastoma may not be palpable on physical examination. The location of the mass on imaging gives a clue to the diagnosis. Although Katie's tumor is located in the most common site, the adrenal gland, a neuroblastoma can occur anywhere along the sympathetic nervous system. These sites include the adrenal glands (>50%), the abdominal paraspinal ganglia (24%), the thoracic paraspinal ganglia (20%), the neck (3%), and the brain (rarely).

The CBC count shows a white blood cell (WBC) count of 10,200/μL (10.2×10^9/L), with 56% neutrophils and 44% lymphocytes. The hemoglobin level is 12 g/dL (120 g/L), and the platelet count is 250×10^3/μL (0.25×10^9/L). Her electrolyte, liver enzyme, and fibrinogen levels and coagulation profile are all normal. Her urinary vanillylmandelic acid (VMA) level is 722 mg/g creatinine (reference range, <25.0 mg/g creatinine) and urinary homovanillic acid (HVA) level is 960 mg/g creatinine (reference range, <35.0 mg/g creatinine). The oncologist explains the laboratory values to the mother and states that the increase *in urinary catecholamine levels combined with the ultrasonography findings raise concern for a neuroblastoma.*

A diagnosis of neuroblastoma is suggested by laboratory, radiologic, and histologic findings (Table 1). Katie's CBC count is normal, without findings of neutropenia, anemia, or thrombocytopenia, which most likely excludes bone marrow involvement. Abnormal liver enzyme levels and coagulation panel values are generally secondary to liver metastasis, which is not the case for Katie. Both VMA and HVA are catecholamine metabolites that are secreted by neuroblastoma cells and are elevated in 90% to 95% of patients with neuroblastomas. Of note, spot or random urinary catecholamine levels are sufficient to make the diagnosis, and a 24-hour urine collection for catecholamine levels is not needed. Although radiologic studies such as ultrasonography or chest radiography are initially used, magnetic resonance imaging (MRI) (preferred) or computed tomography (CT) is required to better evaluate disease burden (Fig 1).

An abdominal MRI demonstrates a 2-cm heterogeneous mass with calcifications arising from the right adrenal medulla. No lymph node or perivascular involvement is noted.

Although Katie's laboratory and MRI findings are favorable for localized disease, a metastatic evaluation is necessary for the management of a neuroblastoma. Indeed, metastatic disease to the bone marrow, liver, and skin is found in approximately 50% of patients during the initial presentation. These patients often present with constitutional symptoms such as fever, malaise, pallor, and fussiness. In addition, there may be refusal to walk/crawl, localized pain, and abdominal distention. A "blueberry muffin rash" is a cutaneous manifestation of a neuroblastoma in infants, representing tumor spread to subcutaneous tissue. These cutaneous nodules are purpuric lesions that blanch on palpation. When examining purpuric subcutaneous nodules, leukemic infiltrates and extramedullary hematopoietic centers must be included in the differential diagnosis because the location and appearance are similar. Orbital findings, including heterochromia irides and periorbital ecchymosis, or "raccoon eyes," are secondary to metastatic spread to the retrobulbar region and are rare but suggestive findings for a neuroblastoma.

TABLE 1. **Laboratory, Radiology, and Pathology Evaluation for Neuroblastoma (6)**

Laboratory	Complete blood cell count with peripheral smear Complete metabolic panel, uric acid Coagulation panel Ferritin and lactate dehydrogenase levels (nonspecific) Urine vanillylmandelic acid and homovanillic acid
Radiology	Initial: chest radiograph or ultrasonography Urgent/emergency: CT scan Preferred: MRI of primary site AND chest, abdomen, and pelvis Metastatic: I-123 metaiodobenzylguanidine scan
Pathology	Bilateral bone marrow aspirate and biopsy with IHC analysis Tumor biopsy with IHC analysis DNA ploidy Fluorescence in situ hybridization for *MYCN* Segmental chromosomal alteration analysis

CT, computed tomographic; IHC, immunohistochemical; MRI, magnetic resonance imaging.

An I-123 metaiodobenzylguanidine (mIBG) scan is used to look for metastatic disease (Table 1). It uses a radiolabeled molecule that possesses structural similarity to noradrenaline and is taken up by neuroblastoma cells. Although mIBG is 99% specific for metastatic neuroblastomas, 10% of neuroblastomas are not mIBG-avid, which can then be detected using positron emission tomography and CT scan. (14)

An I-123 mIBG scan showed uptake in the tumor but was negative for metastatic disease. The oncologist explains that a right-sided abdominal mass in an infant, such as Katie, with elevated urinary catecholamine levels without systemic findings evident on laboratory evaluation is most likely to be a neuroblastoma. Fortunately, Katie is in the favorable age range (<18 months) where she is highly likely to have spontaneous regression of her neuroblastoma. After detailing Katie's low-risk features, the oncologist converses with the mother and recommends monitoring as the best option for Katie.

Approximately half of all neuroblastomas found in infants spontaneously regress. (4)(6) In infants younger than 6 months, there are a few factors that ensure 98% event-free survival with observation alone. These factors include location (primary adrenal location, without metastases), size (<5 cm), clinical aggressiveness (<50% increase in tumor size during the screening phase), and laboratory evidence (<2-fold increase in urinary catecholamine levels starting from the time of diagnosis through the entire observation period). (15) Observation consists of sequential abdominal ultrasonography and urinary catecholamine levels at 6 and 12 weeks, followed by serial screening every 3 months for the first year and every 6 months for the second year. Surgical evaluation and histologic assessment are necessary if the tumor grows during the screening

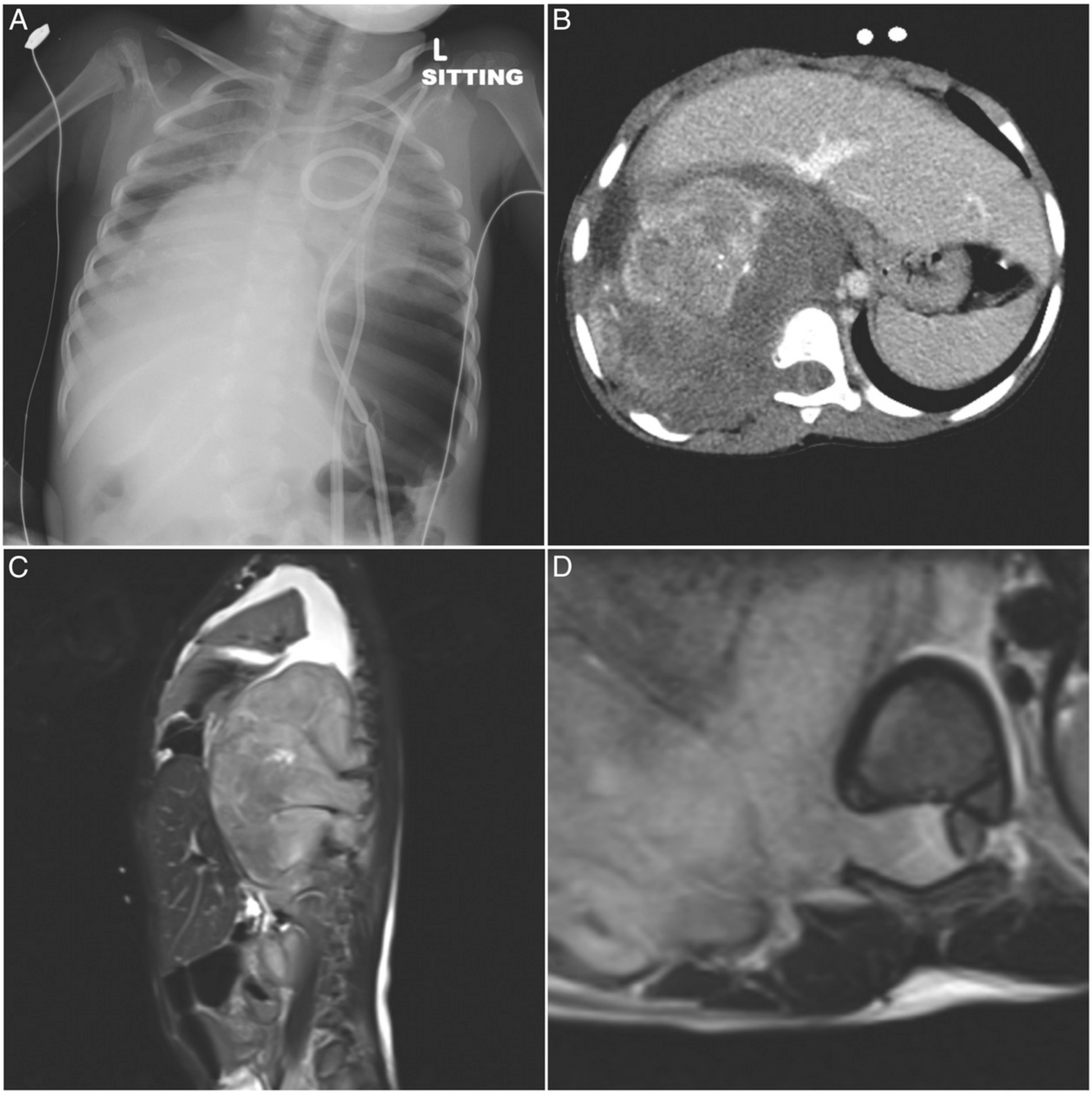


Figure 1. A. Chest radiograph shows a soft tissue mass at the right lung base. B. Computed tomographic scan shows a large right paraspinal mass with partial enhancement, large areas of necrosis, and scattered calcifications. C. Growth of tumor through interpendicular spaces. D. T2-weighted magnetic resonance image demonstrates tumor neuroforaminal invasion in a classic "dumbbell" pattern.

period. This mild presentation is contrasted by the opposite side of the clinical spectrum, as seen in the following 2 cases.

Case 2

Chase is a 3-year-old boy who presents to the pediatrician's office with worsening hip pain, leg pain, and back pain for 3 weeks. He has numbness in both legs, and his mother has noted shortness of breath when he is active. Vital signs are normal in the office. Significant physical examination findings include decreased breath sounds over the right lung, a large nontender abdominal mass, and 1+ Achilles reflex bilaterally. Chase's gait is weak and altered, with dragging of his right leg and frequent falls when taking a few steps. Laboratory results include a WBC count of 9,200/μL (9.2×10^9/L) with a normal differential count, a hemoglobin level of 13.4 g/dL (134 g/L), and a platelet count of 420×10^3/μL (0.42×10^9/L). Electrolyte levels are normal aside from an elevated creatinine level of 1.2 mg/dL (106 μmol/L). Liver enzyme levels and results of coagulation studies are normal. Emergency transport is arranged to take Chase to a pediatric hospital emergency department because of concern for spinal cord compression.

As in this case, a neuroblastoma may present with a clinical sign specific to the location of tumor invasion. Neuroblastoma is one of the most common neoplastic causes of spinal cord compression in children. Common features of spinal cord compression include pain, numbness, and limb weakness. Given that all these signs and symptoms can be subtle in a child, a high index of suspicion is necessary. Sphincter dysfunction, presenting as loss of bowel or bladder function, and loss of deep tendon reflexes are relatively uncommon but ominous signs of spinal cord compression requiring immediate neurosurgical evaluation. An MRI is the most sensitive modality for identifying spinal cord pathology.

A chest radiograph is obtained and demonstrates a large soft tissue mass displacing the right lung (Fig 1A). A contrast abdominal CT scan shows a large lobulated partially enhancing mass with calcifications (Fig 1B). The tumor has displaced nearby structures and collapsed the right lung, with bony destruction of adjacent ribs and the vertebral column (Fig 1C). Spinal MRI depicts the tumor growing through the neuroforamina of the lower thoracic spine and compressing the spinal cord (Fig 1D).

Imaging studies can confirm spinal cord compression. A multidisciplinary approach, involving pediatric oncology and neurosurgery, is required to manage spinal cord compression secondary to a solid tumor. (16) When spinal cord compression is identified, dexamethasone is given with the intent to reduce spinal cord edema while the pediatric oncologist determines definitive therapy. In severe cases, surgical decompression or radiotherapy is used. There is some evidence that the most important component of managing spinal cord compression due to tumor is starting chemotherapy.

Although not seen in this case, pediatricians should also be familiar with 2 syndromes that should raise suspicion for a neuroblastoma. When a neuroblastoma impinges on the oculosympathetic tract, Horner syndrome becomes evident with ptosis, miosis, and anhydrosis. Opsoclonus myoclonus syndrome (OMS) is a paraneoplastic syndrome characterized by rapid multidirectional eye movements, involuntary muscle spasms, and irritability. Although the exact mechanism of OMS remains unknown, an autoimmune reaction is currently the leading hypothesis. Studies have shown the presence of autoantibodies against neuronal and cerebellar Purkinje cells in patients with OMS associated neuroblastoma.

Given the high mortality rate, the painful adverse effects of chemotherapeutic agents, and the long-term effects of high-risk neuroblastoma treatment, palliative care is a key component of comprehensive patient care. More than end-of-life care, palliative care involves control of symptoms while helping the patient live each day to the fullest. Palliative care often starts with the pediatrician, who has the deepest relationship with the patient and family. The pediatrician not only starts the palliation process, which involves quality of life discussions, establishing advance care goals, and providing social, physical, and spiritual support for the patient and family, but also provides an important link to the palliative care specialist.

Case 3

Kurt is a 5-year-old boy who presents to the clinic with fever, fussiness, and decreased activity for 2 weeks. Kurt has lost 2.2 lb (1 kg) since his last visit 4 months ago. On physical examination Kurt is febrile (102.7°F [39.3°C]) and tachycardic. He appears pale and listless. He has bilateral cervical lymphadenopathy, abdominal distention with some tenderness, and petechiae on his extremities. Kurt refuses to stand and starts crying. The CBC count shows a WBC count of 3000/μL (3×10^9/L), with an absolute neutrophil count of 800/μL (0.80×10^9/L), a hemoglobin level of 6 g/dL (60 g/L), and a platelet count of 13×10^3/μL (0.013×10^9/L).

The constellation of pancytopenia, fever, and weight loss raises a concern for a malignancy involving the bone marrow. Because a neuroblastoma commonly metastasizes to the bone marrow, it can present similarly to acute leukemia. A word of caution regarding the abdominal examination is warranted. The presence of ascites may make it difficult to palpate the margins of an abdominal mass. The other frequent abdominal tumor in children is a Wilms tumor. Due to concern for rupture of a Wilms tumor, (17) it is recommended that the abdominal examination not entail deep palpation. In this case, it is sufficient to know that there is no concern for a surgical abdomen and that follow-up imaging to rule out an abdominal mass is needed.

A CT scan of the chest, abdomen, and pelvis shows a large right adrenal mass with widespread lymphadenopathy notably in the right iliac chain, as well as with the right inguinal lymph nodes. The spleen is enlarged. The mIBG scan shows extensive axial and appendicular skeletal uptake (Fig 2). The oncologist performs bilateral bone marrow aspirates and biopsies, which show small clusters of round blue cells, separated by a fibrillar matrix (Homer-Wright rosettes). The small round blue cells are atypical mononuclear cells with irregular nuclei, clumped chromatin, and mostly indistinct nucleoli. Molecular studies from the tumor biopsy show MYCN *amplification, gain of 17q, and hypoploidy. Histopathologic review of the tumor and lymph node biopsy samples demonstrate a stroma-poor, poorly differentiated neuroblastoma.*

Given the wide variance in neuroblastoma behavior, from spontaneous regression (case 1) to metastatic disease (case 3), a rational treatment plan requires risk stratification. Prognostic variables taken into account for stratification are 1) age at diagnosis, 2) stage of disease, 3) molecular alterations, and 4) histopathologic analysis of the tumor. In case 3, Kurt's age at presentation already places him as a

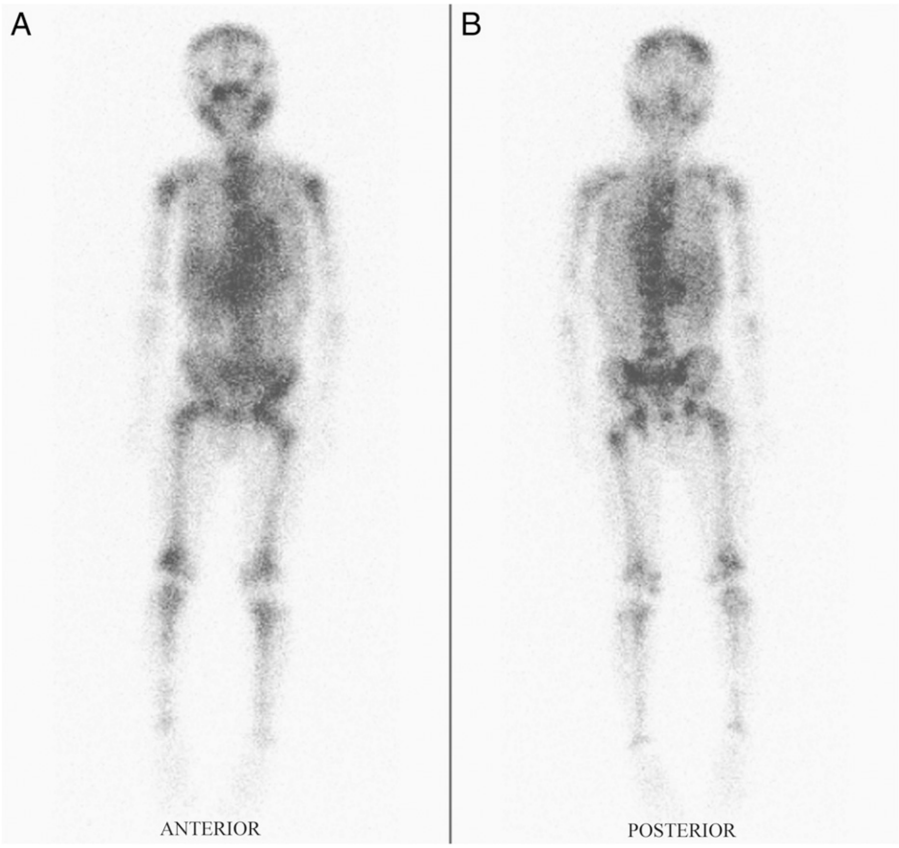


Figure 2. Anterior (A) and posterior (B) I-123 metaiodobenzylguanidine whole body views show abnormal uptake in the bilateral humeri, femurs, and axial skeleton, including the calvarium. There is also uptake in the right upper quadrant consistent with a known neuroblastoma tumor.

high-risk case. Genetic alterations, including *MYCN* amplification, hypoploidy, and the presence of chromosomal alterations, are poor prognostic features. The unfavorable histologic appearance of the tissue biopsy is in concordance with these molecular findings. Given these features, Kurt's case presents as a classic example of a high-risk neuroblastoma, which will require the most aggressive therapy. A detailed discussion of staging and risk stratification of neuroblastoma is beyond the scope of this review, but a brief stratification scheme is provided in Table 2, and excellent reviews have recently been published elsewhere. (6)(18)(19)

NEUROBLASTOMA TREATMENT

A discussion of treatment for high-risk neuroblastoma encompasses all modalities currently in use for pediatric cancer, which include surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy/biological therapy.

Surgery

Surgery was the only treatment available for solid tumors, such as neuroblastomas, before radiotherapy and chemotherapy were used. Because surgery was felt to be definitive treatment, and some neuroblastomas were not able to be surgically resected at the time of diagnosis, the first chemotherapy regimens were designed with an intent to make these tumors operable. (20) Most patients with low-risk neuroblastoma, such as a child with localized disease, favorable histologic findings, nonamplification of *MYCN*, and age younger than 12 months, are, indeed, cured with observation or surgery, when appropriate. (21)(22) However, with high-risk neuroblastoma behavior now elucidated, surgery is an ancillary part of the multimodal treatment. For example, after chemotherapy results in shrinking of the tumor, a second-look surgery is often performed for resection of the tumor. Of note, in a patient with *MYCN* amplification, micrometastases precipitate local recurrence and distant relapse, thereby making surgery alone insufficient for these patients.

Radiotherapy

A neuroblastoma is sensitive to radiotherapy, which has been used in combination with chemotherapy in many earlier neuroblastoma treatment plans. (23) However, radiotherapy carries a risk of late effects, including diabetes mellitus (24) and decreased height potential. (25) More importantly, radiotherapy carries an increased risk of secondary malignancy in

TABLE 2. **International Neuroblastoma Risk Group (INRG) Staging Classifications (19)**

INRG STAGE	AGE, MO	*MYCN*	11Q ABERRATION	PLOIDY	PRETREATMENT RISK GROUP
L1		–			Very low
Localized disease without image-defined risk factors		+			High
L2	<18	–	–		Low
Localized disease with image-defined risk factors		–	+		Intermediate
	≥18	–	–		Low
	≥18	–	+		Intermediate
		+			High
M	<18	–		Hyperdiploid	Low
Metastatic disease	<12	–		Diploid	Intermediate
	12 to <18	–		Diploid	Intermediate
	<18	+			High
	≥18				High
MS		–	–		Very low
Localized primary tumor; dissemination limited to liver, skin, or bone marrow	<18	–	+		High
		+			High

neuroblastoma survivors. (26) This has led to stem cell preparative regimens, which avoid total body irradiation by giving larger doses of chemotherapy. Given the discovery of intermediate-risk neuroblastoma being cured with chemotherapy and/or surgery alone, radiotherapy now is mostly reserved for high-risk neuroblastoma. (27)

Chemotherapy

Chemotherapy remains essential for patients with intermediate- and high-risk neuroblastoma. As with most cancers, to reduce the risk of selecting out cancer populations that become resistant to a single drug, multiagent regimens are used. Common chemotherapeutic agents considered include cyclophosphamide or ifosamide, cisplatin or carboplatin, vincristine, doxorubicin or adriamycin, etoposide, topotecan, and busulfan. The length of treatment has been reduced, and more moderate chemotherapy can be used for intermediate-risk patients. (28) Higher-dose chemotherapy with increased risk of toxicity is prescribed for children with high-risk neuroblastomas. The advent of stem cell transplant has enabled further intensification of chemotherapy for high-risk patients.

Autologous Stem Cell Transplant

Stem cell rescue is accomplished with the patient's own peripheral blood stem cells, infused after a preparative regimen that suppresses the bone marrow. The myeloablative regimen continues to evolve, with variations involving the chemotherapeutic agents used, the number of sequential transplants performed, and perhaps most important for long-term adverse effects, whether radiation is used. In randomized controlled trials, autologous stem cell transplant decreases the risk of relapse by approximately 10%. (27)(29)

Immunotherapy

Fifty percent of children treated for high-risk neuroblastomas, despite achieving initial remission, will relapse. (30) To this end, a maintenance phase was developed involving isotretinoin, anti-GD2 antibody therapy, and cytokines, including granulocyte-macrophage colony-stimulating factor (sargramostim) and interleukin-2 (IL-2). Most familiar to pediatricians in its use for severe acne, isotretinoin is a vitamin A derivative. Also known as 13-*cis*-retinoic acid, isotretinoin acts on neuroblastomas by decreasing tumor cell proliferation and causing differentiation into nonmalignant cells. The attractive aspects of this drug are its ease of administration (given orally) and its relative tolerability. In fact, it can be given for an extended period, even for years. (31) In randomized controlled trials, isotretinoin alone reduces relapse risk at least by 10%, presumably by reducing minimal residual disease, an index used to describe the lowest residual disease burden after chemotherapy that is compatible with a cure, in addition to being used to define relapse.

Given its tolerability, isotretinoin can be combined with more intense maintenance therapy, namely, anti-GD2 antibody therapy. GD2 is one of the few disialoganglioside antigens expressed by most high-risk neuroblastoma cells. (32) The chimeric monoclonal antibody ch14.18 targets the GD2 protein, killing residual neuroblastoma cells via antibody-dependent immune activity. (33) This immune activity is augmented by giving the patient injections of granulocyte-macrophage colony-stimulating factor and by coupling the GD2 antibody with an infusion of IL-2. Given that GD2 is also expressed by peripheral nerve fibers, aggressive pain control is required during its infusion. In addition, the patient must be monitored during the infusion for capillary leak syndrome, which is a severe adverse effect of IL-2. Despite its severe potential adverse effects, the addition of anti-GD2 antibody and IL-2 to isotretinoin has reduced early relapse by approximately 20%, earning its place as part of the current standard therapy for high-risk neuroblastomas.

CONCLUSIONS

Neuroblastoma is a complex disease with diversity of presentation, clinical course, and treatment. Few other diseases may be treated with either intense multimodality treatment or mere observation. When signs and symptoms are recognized early, the pediatrician can help improve outcomes by making a timely referral to the oncologist. Although low-risk groups are highly likely to be cured, the pursuit to improve outcomes for high-risk patients continues. Despite multimodality therapy, cure rates for children with high-risk neuroblastomas remain approximately 50%. More research is needed to delineate treatment targets and new modalities of therapy.

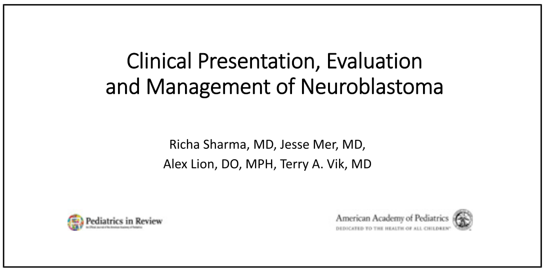
Summary

- On the basis of strong evidence, (2) a neuroblastoma is the most common extracranial solid tumor that requires multifaceted treatment, including observation, surgery, chemotherapy, radiotherapy, autologous stem cell transplant, and immunotherapy.
- Based on strong evidence, (10) neuroblastoma is mostly due to somatic mutations that cause abnormal growth of neural crest cells of the adrenal medulla and sympathetic ganglia.
- On the basis of consensus, pediatricians play a pivotal role in the diagnosis of neuroblastoma. A high index of suspicion is required given the wide spectrum of clinical presentation by neuroblastoma. Neuroblastoma should be considered in children with findings of abnormal breathing, especially when associated with Hirschsprung disease, an abdominal mass, ambulating difficulties, bowel/bladder dysfunction, fever, malaise, bone pain, or abnormal skin findings.
- Based on strong evidence, (6) increased urinary catecholamine levels are highly sensitive for detecting a neuroblastoma, and further evaluation, including laboratory, radiographic, and histologic analyses, are necessary to confirm the diagnosis of a neuroblastoma and to guide medical therapy.

ACKNOWLEDGMENT

We are indebted to the patients and families treated at Riley Children's Hospital.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/4/194.supplemental.



Clinical Presentation, Evaluation
and Management of Neuroblastoma

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Pediatrics in Review

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1. A 15-month-old girl presents to your office with a 3-week history of pain in both legs and refusing to stand, intermittent fever, and bruising. She has a decreased appetite and has lost 3 lb (1.4 kg) in the past 2 to 3 weeks. Vital signs show a temperature of 100.9°F (38.3°C), a pulse of 135 beats/min, a respiratory rate of 20 breaths/min, and blood pressure of 100/52 mm Hg. Physical examination shows an ill-appearing girl with scattered ecchymoses of the extremities and around the eyes. An abdominal mass is palpated in the right flank. Abdominal ultrasonography shows the right kidney to be displaced downward by a suprarenal mass. Which of the following is the most likely diagnosis in this patient?
   - A. Hepatoblastoma.
   - B. Lymphoma.
   - C. Neuroblastoma.
   - D. Ovarian germ cell tumor.
   - E. Wilms tumor.
2. Further evaluation with I-123 metaiodobenzylguanidine (mIBG) scan shows enhancement of the right suprarenal mass with an enhancing mass in the central portion of the abdomen. Multiple areas of osseous uptake are seen in the arms, legs, vertebral bodies, and skull. Which of the following biomarkers is most likely to be elevated in this patient?
   - A. Serum α-fetoprotein.
   - B. Serum β-human chorionic gonadotropin.
   - C. Serum carcinoembryonic antigen.
   - D. Urine 5-hydroxyindole acetic acid.
   - E. Urine vanillylmandelic acid (VMA).
3. The child is taken for biopsy of the abdominal mass and bone marrow aspirate and biopsy. Pathology shows neuroblastoma. Which of the following gene amplifications is most associated with neuroblastoma and is associated with aggressive tumor phenotype and poor prognosis?
   - A. *BRAF*.
   - B. *BCR-ABL*.
   - C. *MDR1*.
   - D. *MYCN*.
   - E. *P53*.
4. A 1-week-old full-term infant is brought to your office for follow-up evaluation. He was found on prenatal ultrasonography to have an abdominal mass in the left suprarenal region. At the time of birth, a magnetic resonance image (MRI) of the abdomen showed a 2.5-cm mass in the left adrenal gland with no other abnormalities seen. An mIBG scan performed while he was in the nursery showed enhancement of the left adrenal mass but no other abnormal enhancement. A complete blood cell count and a comprehensive metabolic panel were normal. Urine for homovanillic acid (HVA) and VMA obtained in the nursery are reviewed and found to be elevated. Which of the following is the most appropriate next step in the management of this infant?
   - A. Immunotherapy with anti-GD2 antibody.
   - B. Isotretinoin.
   - C. Observation with close follow-up.
   - D. Radiotherapy to the mass.
   - E. Surgical resection of the mass.

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5. A 6-week-old infant presents with a 1-week history of vomiting and abdominal swelling. The mother has noted blue to purple nodules on his skin during the past few days. Physical examination shows a well-appearing infant with a temperature of 98°F (36.7°C), a pulse of 110 beats/min, and a respiratory rate of 24 breaths/min. There are several purple, blanching nodules on the skin. The lungs are clear to auscultation. The abdomen is protuberant, with the liver palpated 3 cm below the costal margin. He is moving all extremities. A complete blood cell count shows a white blood cell count of 2,500/μL (2.5×10^9/L), a hemoglobin level of 9 g/dL (90 g/L), and a platelet count of 110,000/μL, with 30% neutrophils, 65% lymphocytes, and 5% monocytes. An MRI with contrast of the abdomen shows a 3-cm mass in the right adrenal gland and an enlarged liver with numerous enhancing nodules. An mIBG scan shows disease localized to the liver and right adrenal gland but without bony involvement. Urine for VMA and HVA showed elevated levels. A biopsy of the skin lesion confirms the diagnosis of neuroblastoma. *MYCN* and chromosomes 1p and 11q are normal. Which of the following represents the stage of neuroblastoma in this infant?
   - A. L1.
   - B. L2.
   - C. Metastatic.
   - D. Metastatic special.
   - E. Not enough clinical information to assign a stage.

Red Blood Cell Distribution Width: Clinical Use beyond Hematology

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INTRODUCTION

The complete blood cell (CBC) count is a widely available and commonly used inexpensive laboratory test used in clinical practice. Information contained therein includes the white blood cell count and differential count, red blood cell (RBC) count, RBC indices, hemoglobin level, hematocrit concentration, and platelet count. The RBC indices include the mean cell volume (MCV), mean cell hemoglobin, mean cell hemoglobin concentration, and RBC distribution width (RDW). (1) Traditionally, the clinical use of RDW has been limited to helping differentiate certain types of anemias (eg, β-thalassemia minor and iron deficiency anemia, which can both have decreased MCV and decreased mean cell hemoglobin but will differ in their RDW). (2) During the past decade, this quick and inexpensive test has been the subject of several studies attempting to evaluate its use as, among other things, an inflammatory marker, (3)(4)(5)(6)(7)(8) a predictor of all-cause mortality, (9)(10) and a prognostic tool for morbidity and mortality associated with sepsis and cardiovascular disease. (4)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25) This article focuses on discussing the RDW as a diagnostic and prognostic tool in various medical conditions.

DEFINITION

What Is the RDW?

Each RBC is shaped as a biconcave disk with a depressed center, its volume ranging from 80 to 100 femtoliters (fL; 1 fL = 10^{-15} L) in adults (represented by the MCV in the CBC count). The RBC membrane is extremely flexible and, in certain conditions, is able to change shape (eg, in hereditary spherocytosis or sickle cell disease) and to decrease or increase in size (eg, microcytosis in the thalassemias, macrocytosis in folate deficiency) without significant cell injury or loss in function. Differences in cell volume among the RBCs, or anisocytosis, is reflected in the CBC count by the RDW. It is calculated by dividing the standard deviation of RBC volumes by the MCV and multiplying the result by 100. (2)

Determinants of the RDW

Erythropoietin, a hormone produced in the kidneys, is primarily responsible for RBC production and maturation in the bone marrow and is a major determinant of the RDW. (2) Abnormal production of erythropoietin (eg, in renal disease) and decreased responsiveness to the hormone (eg, in chronic inflammatory conditions and critical illness) can thus lead to an increase in RDW values. (2)(26)(27)(28)(29) Jelkmann (28)

AUTHOR DISCLOSURE Drs Litao and Kamat have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BNP	brain natriuretic peptide
CBC	complete blood cell
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
FMF	familial Mediterranean fever
MCV	mean cell volume
RBC	red blood cell
RDW	red blood cell distribution width

noted that the proinflammatory cytokines interleukin-1 and tumor necrosis factor-α suppress erythropoietin gene expression.

Many of the conditions for which an increase in RDW was correlated are associated with systemic inflammation and critical illness, but the exact pathophysiologic mechanisms underlying the association of increase in RDW with morbidity and mortality remains unclear. (14) Given that erythropoietin is a key determinant of the RDW, it could perhaps be postulated that any condition affecting erythropoietin activity (eg, inflammation, primary renal disease, heart failure, bone marrow failure) could potentially lead to increased RDW values.

Studies in adults by Miyamoto et al (23) and Rodriguez-Carrio et al (30) have found a significant association between RDW increase and elevated levels of proinflammatory cytokines. Miyamoto et al studied 144 patients with adult congenital heart disease and found that elevated RDW of greater than 15% was significantly associated with elevated serum interleukin-6 levels. (23) Rodriguez-Carrio et al found a positive correlation in patients with rheumatoid arthritis between RDW and serum levels of interferon-α, interleukin-8, vascular endothelial growth factor, and neutrophil to lymphocyte ratio. These support the association of RDW increase with not only systemic inflammation but also vascular remodeling. (30)

Another consideration could be poor nutritional status, often present in patients with chronic diseases or critical illness, or nutrient deficiencies (eg, iron, vitamin B_{12}, or folate deficiency) that are associated with anisocytosis. Other physiologic determinants that have been found to be associated with RDW changes include aging, black ethnicity, and physical exercise. (2)

Note that the use of different hematologic analyzers in different laboratories may result in discrepancies in the measurement of RBC size and in the calculation of the standard deviation of RBC volumes, potentially limiting the use of universal reference ranges and thresholds for RDW values. (2) In 1987, Dr Robert Novak reported normal values of RDW in children (Table 1). (31)

TABLE 1. **Age-Appropriate Values for RDW**

AGE	NO. OF PATIENTS	RDW (MEAN ± SD)
1–6 mo	68	13.0 ± 1.5
7–12 mo	84	13.7 ± 0.9
13–24 mo	108	13.4 ± 1.0
2–3 y	119	13.2 ± 0.8
4–5 y	151	12.7 ± 0.9
6–8 y	106	12.6 ± 0.8
9–11 y	98	12.8 ± 1.0

RDW=red blood cell distribution width.

CLINICAL USES OF THE RDW

Table 2 lists the conditions in children where RDW was found to be elevated.

Anemia

The RDW has traditionally been used, along with the MCV, to evaluate anemias based on morphology. (1)(2) Anemias are typically classified as normocytic, microcytic, or macrocytic, depending on their MCV values. Evaluation of the RDW can further narrow down the potential underlying cause of the anemia. Anemias secondary to nutrient deficiencies (eg, iron deficiency, vitamin B_{12} deficiency, or folate deficiency) are typically associated with marked anisocytosis compared with anemias secondary to genetic defects or primary bone marrow disorders, although significant overlap may occur. (2) Sousa et al, (3) for example, studied 34 pediatric patients with Fanconi anemia, a genetic bone marrow failure syndrome, and found a significant increase in RDW in 68% of patients, noting a correlation with anemia, neutropenia, and thrombocytopenia, concluding that significantly increased RDW is associated with progression of Fanconi anemia disease.

Hemolytic anemias, except in acute hemolysis, is associated with anisocytosis (eg, in microangiopathic hemolytic anemia). (1)(2) Sazawal et al (32) studied 1,026 children with iron deficiency anemia, finding that the sensitivity of a combined hemoglobin level of 10 g/dL or less (≤100 g/L) and RDW greater than 15% in diagnosing the disease was 99%, with specificity of 90%. Thus, simply getting a hemoglobin level and evaluating the RDW is a cost-effective way to diagnose iron deficiency anemia in children without the need for further and more expensive testing of iron status markers. (32)

Autoimmune Diseases

Increased RDW has been reported to reflect systemic inflammation. (33) Studies in adults(34)(35)(36) have found a correlation between increased RDW and disease activity in rheumatoid arthritis, proposing that RDW could be used as an inflammatory marker, similar to the more traditionally used erythrocyte sedimentation rate (ESR) and C-reactive

TABLE 2. **Pediatric Conditions Associated with Elevated RDW**

ANEMIAS	AUTOIMMUNE DISEASE	CARDIAC	NEONATES	OTHERS
Anemia associated with nutritional deficiencies (iron, vitamin B_{12}, folate)	Familial Mediterranean fever	Postoperative morbidity and mortality in congenital heart disease	Sepsis	Sepsis[a]
Hemolytic anemia (except acute hemolysis)		Heart failure	Patent ductus arteriosus	Acute appendicitis
Fanconi anemia		Acute rheumatic carditis	Bronchopulmonary dysplasia Early mortality	All-cause morbidity and mortality in critical illness

RDW=red blood cell distribution width.

[a] *Conflicting studies, see Table 3.*

protein (CRP). As mentioned earlier, positive correlations have been reported between increased RDW and levels of certain proinflammatory cytokines. (23)(30)

Ozer et al studied 153 children with familial Mediterranean fever (FMF) to investigate potential markers of subclinical inflammation in these patients. They found that mean ± SD RDW was significantly higher in symptom-free patients with FMF (14.89 ± 2.56) compared with a control group of 90 volunteers (13.68 ± 2.35). (5) A study by Yildirim et al (6) conducted in adults with FMF yielded similar results, with significantly higher RDW levels in symptom-free patients with FMF compared with a control group.

Hu et al (7) noted increased RDW in adult patients with systemic lupus erythematosus, and glucocorticoid treatment decreased RDW values. Zou et al (8) reported significantly increased RDW in patients with active systemic lupus erythematosus disease, irrespective of anemia status, with significantly greater flare-free survival within a year in those with normal RDW. These studies have found various degrees of positive correlation between RDW and ESR, (6)(7) between RDW and CRP, (5)(7) and between RDW and high-sensitivity CRP. (8)

Significantly higher RDW has also been reported in adults with active inflammatory bowel disease compared with those without active disease and controls. (37)(38) Similar observations have been found between increased RDW and disease activity in other autoimmune disorders, including ankylosing spondylitis, (39)(40) primary Sjogren syndrome, (41) polymyositis, (42) and multiple sclerosis. (43)(44)

Sepsis

Elevated RDW has been associated with increased morbidity and mortality in patients with severe sepsis and septic shock. Several adult studies have proposed it as a potentially useful prognostic marker in this population. (13)(14)(15)(33) However, there are few pediatric studies that have evaluated RDW in sepsis, and results have been conflicting.

Chen et al (11) retrospectively studied the relationship of RDW with disease severity and prognosis in 97 newborns admitted for sepsis to a hospital in China. Patients were divided into 3 groups depending on sepsis severity (sepsis group, severe sepsis group, and septic shock group). Significant differences in RDW were found among the 3 groups: mean ± SD RDW in the sepsis group was 16.59 ± 1.71, in the severe sepsis group was 18.88 ± 1.78, and in the septic shock group 19.71 ± 1.97. The mortality rate was higher in those with elevated RDW (defined as RDW >18%) compared with those with normal RDW (91.76% versus 49.32%). Further statistical analysis found a significant positive correlation between RDW values and mortality (Table 3). (11)

In contrast, a cross-sectional Indonesian study by Devina et al (12) found no significant differences in mortality rates between those with elevated RDW (defined as RDW >14.5%) and those with normal RDW in a population of 40 pediatric patients with sepsis (age range, 2 months to 17 years; median age, 34 months) (Table 3). They also did not find a significant association between increased RDW and length of stay in the ICU. (12)

Ramby et al (16) retrospectively studied 596 patients (age range, 1.5–12.9 years; median age, 4.4 years) admitted to the PICU and found that RDW was independently associated with overall PICU mortality (odds ratio, 1.25; 95% confidence interval, 1.09–1.43). An association with sepsis-specific mortality was not studied, but RDW was not

TABLE 3. **Conflicting Studies on the Association of Elevated RDW and Sepsis**

SOURCE	POPULATION	FINDINGS
Chen et al (11)	97 newborns admitted for sepsis to a hospital in China	Increased mortality rate in those with elevated RDW >18%
Devina et al (12)	40 pediatric patients admitted for sepsis (age range, 2 mo to 17 y; median age, 34 mo) in a hospital in Indonesia	No significant difference in mortality rates between those with elevated RDW >14.5% and those with normal RDW No significant association between increased RDW and ICU stay
Ramby et al (16)	596 pediatric patients (age range, 1.5–12.9 y; median age, 4.4 y) admitted to the ICU in a US hospital; 111 with sepsis	No significant association between increased RDW and prolonged ICU stay in patients with sepsis

RDW=red blood cell distribution width.

found to be associated with a prolonged (>48 hours) PICU stay in patients with sepsis. (16) (Table 3)

Cardiac Conditions

Congenital Heart Disease. There are several studies on the association of RDW with surgical outcomes in children with congenital heart disease. Massin (21) studied 688 children undergoing surgery for congenital heart disease and found that RDW was a strong predictor of adverse outcomes in these children, correlating with ICU stay and postoperative death. The mean ± SD preoperative RDW of those who died during their postoperative hospital stay was 18.34 ± 4.68, which was significantly higher than the RDW of those who survived (16.12 ± 2.84). Postoperative death risk was 5 times higher for patients with an RDW of 16% or more. (21) A study by Polat et al (24) had similar results, concluding that RDW could be used as a significant predictor of morbidity and mortality in postoperative patients with congenital heart disease.

Similarly, Kumar et al (20) found that elevated RDW was associated with delayed postoperative recovery in children with tetralogy of Fallot. Those with an RDW greater than 17.8% had significantly longer ICU stays, hospital stays, and ventilation time and more surgical site infections.

Kojima et al, (19) in a study of 38 patients with a Fontan circulation who underwent routine cardiac catheterization, found a strong positive correlation between RDW and central venous pressure and a strong negative correlation between RDW and mixed venous oxygen saturation. In fact, the brain natriuretic peptide (BNP) level, which is a common marker used to monitor heart failure in the pediatric population, was not found to have a significant relation with central venous pressure or mixed venous oxygen saturation, whereas the RDW was found to be a significant independent predictor of these. This highlights the potential of RDW as a convenient and inexpensive marker to detect heart failure in patients with a Fontan circulation.

Acquired Heart Disease. Multiple studies have supported the association of elevated RDW with cardiovascular diseases in adults, including acute coronary syndrome, stroke, peripheral artery disease, atrial fibrillation, heart failure, and hypertension. (17)(45)(46) The lower incidence of cardiovascular diseases in children perhaps explains the relative lack of pediatric studies, but Kucuk et al (4) evaluated RDW in pediatric patients with acute rheumatic carditis. The mean ± SD age of patients in their study was 11.6 ± 2.5 years; RDW was found to be significantly higher in those with acute rheumatic carditis compared with a control group, and significantly decreased (along with CRP level, ESR, and platelet count) after 8 weeks of anti-inflammatory treatment. There was also a significantly positive correlation between RDW and the severity of mitral regurgitation in the patient group. The authors concluded that elevated RDW after initial treatment could indicate ongoing subclinical inflammation, which could lead to subsequent valvular stenosis. (4)

Heart Failure. Forhecz et al (47) found that RDW was an independent predictor of all-cause mortality in adult patients with heart failure. Correlations were found between RDW and levels of serum iron, ferritin, soluble transferrin receptor, interleukin-6, soluble tumor necrosis factor receptors I and II, CRP, prealbumin, total cholesterol, albumin, and renal function, indicating the association of RDW with inflammation, undernutrition, ineffective erythropoiesis, and impaired renal function. (47)

Mawlana et al (22) studied 31 pediatric patients with heart failure (mean ± SD age, 16.16 ± 14.97 months; 58.1% with congenital heart disease with left-to-right shunts, 41.9% with dilated cardiomyopathy) and found that RDW greater than 16.4% was significantly correlated with certain echocardiographic markers of left ventricular function, such as fractional shortening and E/A ratio, although the same relationship was not present with left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and E/É ratio. (22)

The results of a 2014 systematic review reinforced the value of RDW as a prognostic indicator in patients with heart failure. (18)

Pulmonary Disease

Ozgul et al (48) studied 175 adult patients with chronic obstructive pulmonary disease (COPD) and found that mean ± SD RDW was significantly higher in these patients compared with a control group (15% ± 2.3% versus 13.8% ± 2.5%). In the patients with COPD, RDW was found to correlate positively with CRP, albumin, right ventricular dysfunction, pulmonary hypertension, and the presence of cardiovascular disease. Elevated RDW was independently associated with right ventricular dysfunction. (48) Although COPD is not a pediatric disease, research delving into the potential use of RDW as an inexpensive prognostic marker in pediatric pulmonary hypertension could be helpful. N-terminal proBNP is a commonly used marker to monitor right ventricular dysfunction and heart failure in neonates with pulmonary hypertension, but it is a very expensive laboratory test and is not typically available in smaller hospitals. The previously mentioned study by Kojima et al (19) found RDW to be a significant predictor of central venous pressure independent of the BNP, so further studies into its use in pediatric pulmonary hypertension could be of value.

Other Illnesses

A retrospective study by Ramby et al (16) of 596 critically ill pediatric patients found an association between RDW and prolonged PICU stay in those without sepsis, with a 1.17 increased odds for each 1% increase in RDW. Patients with an RDW less than 13.4% had a 53% risk of a PICU stay greater than 48 hours and a 3.3% risk of mortality, whereas those with an RDW greater than 15.7% had a 78% risk of a PICU stay longer than 48 hours and a 12.9% risk of mortality. (16)

In a study by Garofoli et al, (49) preterm newborns with patent ductus arteriosus, late-onset sepsis, and bronchopulmonary dysplasia were all associated with significantly higher RDW levels compared with preterm newborns without these pathologies. Elevated RDW in preterm newborns and infants with intrauterine growth restriction was also found to be significantly associated with early mortality. (49)

A study by Yilmaz et al (50) found significantly higher RDW levels in adults with preeclampsia compared with controls. The RDW was also significantly higher in those with severe preeclampsia compared with those with mild preeclampsia. Given the increased rates of pregnancy-associated hypertension and eclampsia in teenage pregnancies, monitoring the CBC count and RDW in this population may be useful.

Bozlu et al (51) studied the diagnostic utility of RDW in children with acute appendicitis, retrospectively evaluating 344 children who underwent appendectomy. Children with simple or perforated appendicitis had significantly higher white blood cell counts, CRP levels, and RDW levels than those with a normal appendix, but there was no significant difference in RDW values between those with simple versus perforated appendicitis. The diagnostic utility of RDW in pediatric patients with acute appendicitis was thus concluded to be low because it was not found to be superior to white blood cell count, which is also included in a CBC count; nor was it of value in predicting perforated appendicitis.

Other conditions that have been found to have an association with elevated RDW in adult studies include cancer, diabetes mellitus, kidney disease, liver disease, and complicated community-acquired pneumonia. (2)

CONCLUSIONS

The RDW, as part of the CBC count, is routinely assessed when evaluating anemias. However, as evidenced by recent studies, it may also be an inexpensive method to assess the prognosis and clinical status of critically ill patients, those with inflammatory disorders (eg, FMF), and those with cardiac disease (eg, heart failure, acute rheumatic carditis, postoperative patients with congenital heart disease), particularly in resource-limited settings. Several studies in adults, and a few in children, have supported the role of an elevated RDW in these conditions. Although the prognostic utility of an elevated RDW in adult patients with sepsis has been substantiated by multiple studies, those performed in children have had conflicting results. Other adult studies have found an association between elevated RDW and cancer, diabetes mellitus, kidney disease, liver disease, and complicated community-acquired pneumonia. Pediatric studies in these areas are currently lacking. Further studies on the diagnostic and prognostic uses of the RDW in different pediatric conditions, particularly those involving infection, inflammation, cardiac, and perhaps cardiopulmonary disease, would be of great benefit.

References for this article are at http://pedsinreview.aappublications.org/content/39/4/204.

Index of Suspicion

1 Eye Discharge in a 10-day-old Neonate Born by Cesarean Delivery

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Singh, Galvis, and Das have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-day-old boy presents with discharge from the left eye. It started at 3 days of age as a continuous, clear discharge and became copious and mucopurulent at 7 days of age. The mother reports swelling over the left eye, which started 2 days ago, and it worsened gradually so that he is not able to open his left eye today. The mother denies fever, trauma, sick contacts, recent travel, or rash. The patient was born at term via cesarean delivery. Maternal history is significant for a *Trichomonas vaginalis* infection during the second trimester, which was adequately treated. All other prenatal test results were negative. Review of the nursery records revealed that the patient received erythromycin prophylaxis for conjunctivitis.

On admission, he is afebrile and his vitals are stable. Physical examination shows a fussy neonate with eyelid swelling and erythematous conjunctiva with mucopurulent discharge from the left eye. The remaining physical examination findings are normal.

Initial laboratory evaluation shows a normal complete blood cell count and serum electrolyte levels. His human immunodeficiency virus (HIV) antibody test as well as rapid plasma reagin test results are negative. The cerebrospinal fluid (CSF) analysis results are normal. Additional evaluation leads to the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/210.

DISCUSSION

The differential diagnosis of injected conjunctiva with eye discharge (conjunctivitis) in the neonatal period includes chemical conjunctivitis, chlamydia conjunctivitis, gonococcal conjunctivitis, and trauma. Gram-stain of the discharge from the left eye of our patient showed gram-negative diplococci, which were confirmed to be *Neisseria gonorrhoeae* on culture. Chlamydia polymerase chain reaction was negative. Blood, urine, and CSF cultures were sterile.

The patient was initially started on intravenous ampicillin and cefotaxime pending culture results. The antibiotics were discontinued after 48 hours when the blood, urine, and CSF cultures were reported to be negative. However, after the culture result from the left eye was confirmed to be *N gonorrhoeae*, the patient was treated with a single dose of ceftriaxone and underwent scheduled irrigation of both eyes. The patient was evaluated by a pediatric ophthalmologist to ensure that he has not developed the complications of gonococcal conjunctivitis, and none were identified. The patient responded well, with complete resolution of the swelling and mucopurulent discharge. The mother and her partner were requested to get evaluated and treated for sexually transmitted infections (STIs).

The Condition

Ophthalmia neonatorum (ON), also called neonatal conjunctivitis, is a broad term and includes all forms of acute, mucopurulent infection of the eyes in the first 4 weeks of life. Up to 12% of newborns are affected by ON. In the past (before the 1880s), the term *ON* was used only for cases of conjunctivitis caused by infection with *N gonorrhoeae* and was the primary cause of neonatal blindness. (Table)(1)

TABLE. **Causes of ophthalmia neonatorum**

• **CHEMICAL**	• **VIRAL**
• **Bacterial**	• *Adenovirus*
• *Chlamydia trachomatis*	• *Herpes simplex virus*
• *Neisseria gonorrhoeae*	
• *Haemophilus species*	
• *Streptococcus pneumoniae*	
• *Staphylococcus aureus*	
• *Staphylococcus epidermidis*	
• *Streptococcus viridans*	
• *Escherichia coli*	
• *Pseudomonas aeruginosa*	
• Other	

Epidemiology

Chlamydial infections are the most common bacterial cause of conjunctivitis in neonates, accounting for up to 40% of cases of neonatal conjunctivitis. *Streptococcus pneumoniae* and nontypeable *Haemophilus influenza* have been estimated to account for 30% to 50% of cases of ON, whereas *N gonorrhea* accounts for less than 1% of cases of ON in the developed world. In the United States, perinatal transmission occurs in 30% to 40% of patients with maternal cervical infection. (2) Intrauterine transmission is also possible after the rupture of membranes.

Gonococcal infection in neonates born by cesarean delivery is rare. The first case of gonococcal conjunctivitis after cesarean delivery was described by Thompson et al in a case series of 7 patients in 1974. (3)

A variety of mechanisms have been proposed to explain the transmission of gonococcal infection in newborns born via cesarean delivery, as discussed. (4) One of the suggested modes of transmission is spread of infection from the infected birth canal to the amniotic fluid during a period between rupture of membranes and birth of the neonate. It is also possible to have postnatal transmission of infection from maternal genitalia to neonatal eyes by person-to-person transmission. (4) In another study, Handsfield et al found neonatal orogastric contamination with *N gonorrhoeae,* suggesting intrauterine infection. (5)

Prophylaxis

Historically, the introduction of postnatal prophylaxis with 2% silver nitrate decreased the incidence of neonatal gonococcal conjunctivitis from 10% to 0.3%. (1) A need for prophylaxis is under debate because of the decreasing incidence of STIs, effective treatment for conjunctivitis, and risk of developing resistance to antibiotic agents. Currently, the standard of care in the United States is the use of topical erythromycin ointment for prophylaxis. However, although the use of postnatal prophylaxis decreases the incidence of transmission, it does not completely eliminate it. (1)

Microbiology and Pathogenesis

Neisseria gonorrhoeae is an intracellular gram-negative diplococci. The outer membrane of *N gonorrhoeae* contains lipooligosaccharide, phospholipid, and a variety of proteins, including the porin (PorB) protein. PorB is essential for bacterial viability because it mediates ion exchange between *N gonorrhoeae* and the environment. PorB has also been implicated in being crucial for the pathogen to evade both the innate and adaptive immune systems. There are 2 alleles for PorB, known as PIA and PIB, that are associated with different phenotypes. The PIA strains are associated with disseminated disease because these strains are resistant to the bactericidal effects of human serum, and the PIB strains are associated with localized urogenital infections. (6)(7)(8) Initial attachment of gonococci to the surface of columnar epithelial cells is mediated by type IV pili. After attaching to mucosal cells, gonococci are engulfed in a process known as parasite-directed endocytosis, and the gonococci proceed to replicating intracellularly. The bacteria can then extend through lymphatics or can cause bacteremia, leading to disseminated disease.

Clinical Features

Infection usually is manifested 2 to 5 days after birth. It causes purulent conjunctivitis, with profuse exudate and swelling of the eyelids. If untreated, severe complications such as corneal scarring, blindness, and septicemia can occur.

Diagnosis

Gonococcal conjunctivitis is diagnosed by prenatal and perinatal history, physical examination, and microbiologic examination of conjunctival exudate. A Gram-stain of the conjunctival exudate should be examined for the presence of typical gram-negative intracellular kidney bean–shaped diplococci. For identifying *N gonorrhoeae* from nongenital sites, culture is the most widely used test. The patient should also be evaluated for chlamydia trachomatis, congenital syphilis, and HIV infections because of an increased incidence of coinfections with these pathogens. The mother's hepatitis B status should also be investigated. In addition, the patient's mother and her sexual partner should be evaluated for gonococcal and other STIs. (9)

Treatment

Infants suspected of having gonococcal ophthalmic disease should be hospitalized and observed for response to therapy and for disseminated disease (sepsis, arthritis, meningitis). After obtaining cultures (from eye, blood, urine, and CSF), empirical treatment should be started in patients in whom organisms are seen on Gram-stain or in those with negative Gram-stain but who are considered to be at high risk (eg, a mother with no prenatal care, history of STIs, or substance abuse). The current guidelines recommend treatment of neonatal gonococcal conjunctivitis with a single dose of ceftriaxone 25 to 50 mg/kg, with a maximum of 125 mg given intravenously or intramuscularly. (9) Furthermore, patients require frequent irrigation of the eye with saline until resolution of discharge from the affected eye. (9) Topical antimicrobial therapy alone is not adequate to treat gonococcal conjunctivitis. Treatment of ON should be continued beyond the single treatment dose until all bacterial cultures are negative and systemic infection has been excluded, typically after 48 to 72 hours of therapy.

Lessons for the Clinician

- Clinicians should have a high index of suspicion for serious bacterial infections, such as infections with *Neisseria gonorrhoeae,* as the cause of neonatal conjunctivitis even in neonates born via cesarean delivery.
- Clinicians should start with systemic antibiotic drug treatment when gonococcal conjunctivitis is suspected.
- One should closely monitor neonates for ophthalmologic and systemic complications of gonococcal conjunctivitis.
- All newborns should be provided topical antibiotic drug prophylaxis at birth.

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2 Jaw Pain, Pain on Deep Inspiration, and Severe Odynophagia in an 18-year-old Boy

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AUTHOR DISCLOSURE Drs Mangan, Shah, Troy, and Dawgert have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-year-old boy presents with right-sided jaw pain, migratory body pains, decreased appetite, pain on deep inspiration, severe odynophagia, and dark urine. He had no history of sick contacts or international travel. He was evaluated a week earlier for a sore throat, moderate dysphagia, fever, and decreased energy. On physical examination at that time he was found to have an erythematous posterior pharynx, moderately enlarged tonsils, and cervical lymphadenopathy. His streptococcal antigen and Monospot test results were negative. He was prescribed corticosteroids and naproxen for pain and severe tonsillar enlargement.

Physical examination shows an erythematous posterior pharynx without exudates, severely enlarged tonsils, pleuritic chest pain on deep inspiration, and right mid-thoracic paraspinal tenderness. Vitals on presentation are a

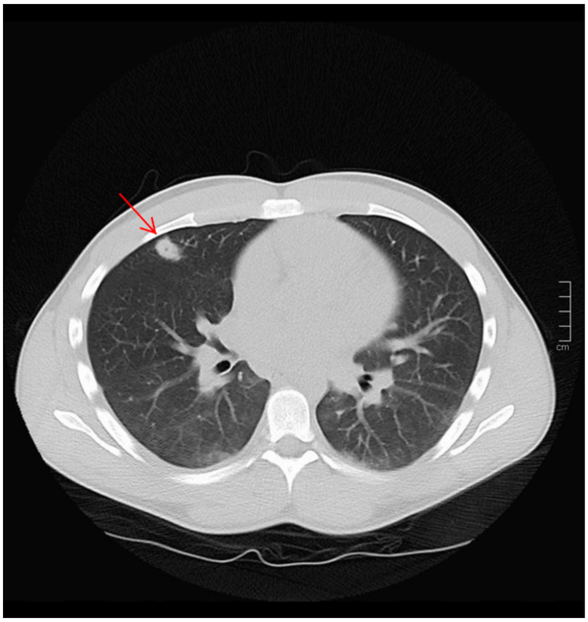

Figure 1. Axial computed tomographic scan of the thorax demonstrates an ovoid nodule (red arrow) in the right middle lobe with a small focus of central cavitation suspicious for a septic embolus.

temperature of 102.4°F (39.1°C) and a heart rate of 90 beats/min. The remaining physical examination results are normal.

He is hospitalized for further evaluation and treatment with ceftriaxone for concern for peritonsillar abscess.

Laboratory evaluation shows a white blood cell count of $24\times10^3/\mu L$ with 60% neutrophils and 25% bands, a platelet count of $115\times10^3/\mu L$ ($115\times10^9/L$), a blood urea nitrogen level of 30 mg/dL (10.7 mmol/L), and a creatinine concentration of 1.1 mg/dL (97.2 μmol/L). Urinalysis shows trace ketones, 5 to 9 red blood cells per high-power field, a urobilinogen level of 8 mg/dL, 2+ bilirubin, and 1+ protein. A chest computed tomographic (CT) scan is performed because of pleuritic chest pain and shows interstitial pneumonia with possible septic emboli along with mediastinal and hilar lymphadenopathy (Fig 1). After 3 days, blood cultures are negative.

Given continued symptoms 3 days later, he is transferred to a tertiary care center, where additional imaging studies revealed the final diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/211.

DISCUSSION

At the tertiary care center he developed acute respiratory distress, inability to turn or lift his head, and reduced leftward neck rotation and extension, with pain near the sternocleidomastoid in the region of the internal jugular vein. Pulmonary examination showed shallow tachypnea with decreased inspiratory effort and scant expiratory wheezes over the left lower lobe.

A CT of the neck with intravenous (IV) contrast showed a thrombosis of the middle segment of the right internal jugular and right parapharyngeal veins with surrounding edema and inflammation (Fig 2). With the jaw tenderness, internal jugular and parapharyngeal vein thrombophlebitis, and fever, the patient was diagnosed as having Lemierre syndrome and was transitioned to IV clindamycin from ceftriaxone. The patient's blood cultures grew *Fusobacterium necrophorum*. After 2 days he did not show much improvement so his antibiotics were changed to IV meropenem. He was discharged 2 days later in fair condition. The patient went home on IV meropenem 1 g every 8 hours for 6 weeks, enoxaparin 80 mg/0.8 mL subcutaneously every12 hours, and *Lactobacillus rhamnosus* as a probiotic 2 times a day. The decision was made to send the patient home on enoxaparin to reduce his risk of further thrombosis and to allow for his current clot burden to dissipate.

THE CONDITION

Lemierre syndrome was first described in 1936 by French microbiologist Andre Lemierre, who came across 20 patients who had sepsis, metastatic pulmonary lesions, and *Bacillus funduliformis* (now known as *F necrophorum*). (1) This rare infectious syndrome is most commonly caused by *F necrophorum*, a gram-negative anaerobic bacillus that is part of the normal human oral flora. (1) The pathophysiology of this syndrome is unclear, and it is not known why *F necrophorum* becomes invasive. (2)

Lemierre syndrome was once a more common disease until the advent of antibiotics. Before the wide use of penicillin, Lemierre syndrome carried with it mortality of close to 90%. (1) Once the advent of penicillin occurred, this disease became virtually extinct. Between 1974 and 1995 there were only 100 published cases of Lemierre syndrome. (4) However, in the late 1990s the disease began a resurgence, and its incidence has near doubled and has continued to rise. There are 2 hypothesizes as to why Lemierre syndrome is reemerging, the first of which is that clinicians are trying to avoid unnecessary antibiotic drug use in pharyngitis that follows a typical viral pattern or in patients with a negative rapid streptococcal antigen test result. (1)(3) The second hypothesis is simply that the reporting of Lemierre syndrome increased and that the incidence of the disease was at its current level. (1)

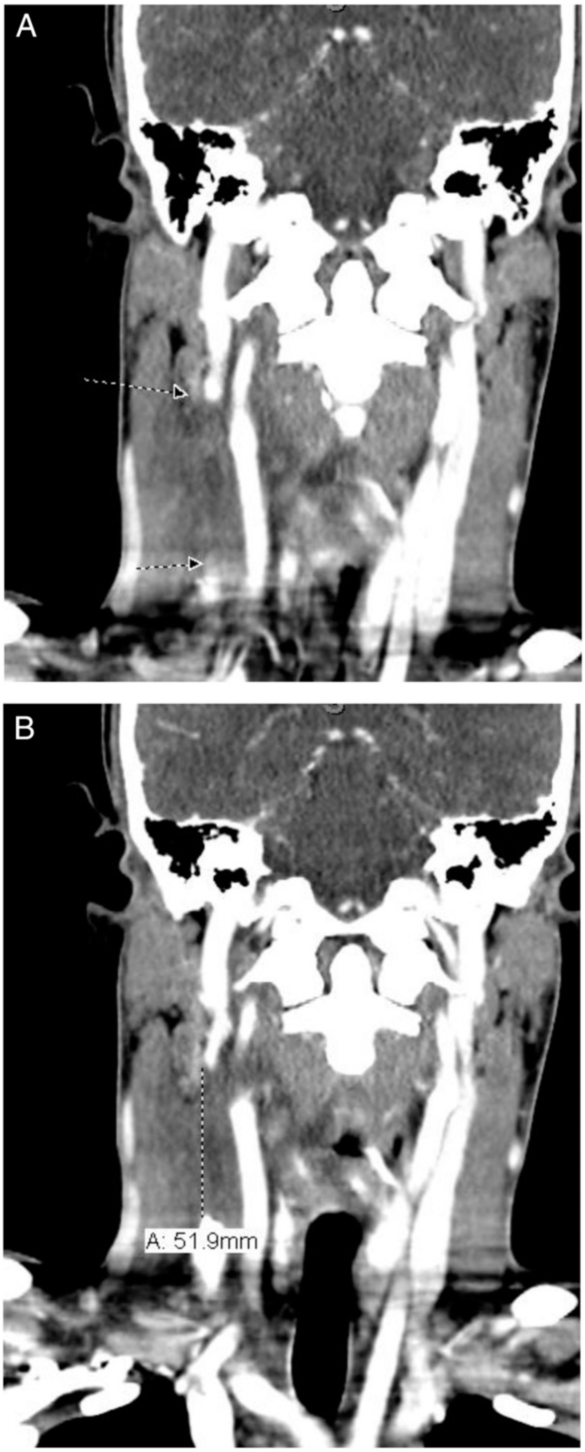

Figure 2. A. Reconstructed coronal computed tomographic scan of the neck with contrast demonstrates an intraluminal filling defect in the right internal jugular vein (arrows). B. The length of occlusion in the internal jugular vein was measured to be 51.9 mm. This filling defect is compatible with thrombus formation.

In 2010, it was estimated that pharyngitis caused by *F necrophorum* may be as common as that caused by group A streptococcus. (5) Furthermore, 1 in 400 cases of *F necrophorum* infection lead to complications, which include abscess, septicemia with pulmonary emboli, and Lemierre syndrome. (5) Case series have shown mortality associated with *F necrophorum* of 3% to 5% and morbidity of 10%. (5) Although the incidence of the disease has been increasing, it still remains a rare cause of pharyngitis. At this juncture it does not warrant treating all streptococcal antigen test–negative pharyngitis with antibiotic agents. This disease most commonly affects healthy adolescents and young adults, with a higher incidence in the winter and spring. (1) However, as demonstrated by the present case, the disease does not follow a strict seasonal pattern. The most common presenting symptom is pharyngitis, which usually precludes all other symptoms for 4 to 5 days. (1) On physical examination patients usually have a fever and may have a peritonsillar abscess. Symptoms typically progress over the next 5 to 12 days, with the development of neck pain, pleuritic chest pain, dyspnea, night sweats, and possible arthralgia. (1) Patients rapidly develop signs of endovascular septicemia, with tachycardia, fever, and leukocytosis. (2) The differential diagnosis includes infectious and malignant etiologies (Table 1). Lemierre syndrome is a clinical diagnosis based on the findings of gram-negative anaerobic bacteremia, metastatic septic pulmonary emboli, and thrombophlebitis of the internal jugular vein. Various imaging modalities are important to use to identify disease-defining pathology. Commonly, a chest CT scan is helpful in differentiating causes of pleuritic chest pain such as infection and malignancy. Ultrasonography of the neck can help identify any thrombosis in the jugular venous system. Other diagnostic imaging can be helpful in identifying and treating other manifestations of this disease, such as meningitis and septic arthritis.

TABLE 1. **Differential diagnosis based the presentation and progression of the signs and symptoms of Lemierre's Disease.**

DIFFERENTIAL DIAGNOSIS
• Pyelonephritis
• Pharyngitis
• Viral URI
• Torticollis
• Uro-Sepsis
• Mononucleosis
• Pharyngeal/Tonsillar Abscess
• Lymphoma
• Tuberculosis

MANAGEMENT

Treatment of Lemierre syndrome requires 4 to 6 weeks of antibiotic drug therapy. (1) The antibiotic of choice is penicillin for Lemierre syndrome. (1)(5) It is important to note that *F necrophorum* is not sensitive to macrolides, which is the typical treatment for a penicillin-allergic patient with pharyngitis. (5) Therefore, if neck swelling occurs or there is progression of the symptoms the patient should be treated with clindamycin, metronidazole, imipenem, amoxicillin-clavulanate, or cefoxitin. (6) Surgical treatment for the removal of thrombosis is controversial, but abscesses may need to be drained. (1) Anticoagulation therapy is also controversial and not widely used. (1)

Lessons for the Clinician

- Pharyngitis caused by *Fusobacterium necrophorum* is thought to be as common as that caused by group A streptococci and carries with it a different set of complications, which can lead to significant mortality and morbidity. However, at this time, Lemierre syndrome remains rare and does not warrant prophylactic treatment.
- It is important to consider this diagnosis when pharyngitis does not follow the typical course seen with group A streptococcal infection.
- The typical patient with Lemierre syndrome is a young healthy adolescent or young adult with fever, pharyngitis, and a progressive clinical course that includes septicemia, metastatic septic pulmonary emboli, and thrombophlebitis of the internal jugular vein.
- The treatment for penicillin-allergic patients includes clindamycin and not macrolide if infection with *Fusobacterium* is suspected.

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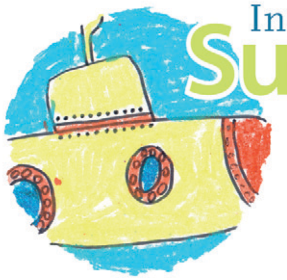

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3 Persistent Pharyngitis in a 14-year-old Girl

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AUTHOR DISCLOSURE Drs O'Halloran and Winn have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-year-old girl is admitted to the hospital with a 3-week history of sore throat leading to significantly decreased oral intake. She reports progressive worsening of a painful sore throat resulting in avoidance of nearly all oral intake and an associated 22-lb weight loss. She has presented to care twice, 2 weeks and 2 days earlier. During each of those visits, rapid group A streptococcal (GAS) antigen testing and follow-up GAS culture were negative. She was discharged with symptomatic care for presumed viral pharyngitis. She vomited twice but has not had fevers, cough, rash, or diarrhea. Her medical history is noncontributory. Her immunizations are up to date. She reports one lifetime sexual partner and reports condom use with every encounter.

On examination the patient is tachycardic to 150 beats/min, afebrile, and other vital signs are normal. Her mucous membranes are dry. She has posterior and anterior cervical lymphadenopathy, palatal petechiae, and erythematous enlarged tonsils with mild exudates. Results of cardiac, pulmonary, abdominal, and complete neurologic examinations are normal.

Initial laboratory tests are notable for an elevated white blood cell count of 20,500/μL (20.5×10^9/L), a sodium level of 154 mEq/L (154 mmol/L), a blood urea nitrogen level of 32 mg/dL (11.4 mmol/L), and a creatinine level of 1.03 mg/dL (91 μmol/L) (her baseline creatinine level is 0.4 mg/dL [35 μmol/L]). Further laboratory testing reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/213.

DISCUSSION

Clinical Course and Management

The patient's fractional excretion of sodium was 0.2%, and, therefore, her acute kidney injury and hypernatremia were thought to be consistent with dehydration and a prerenal state. Both resolved with appropriate fluid resuscitation. An otorhinolaryngologist performed a bedside nasal endoscopy and laryngoscopy, which revealed thick yellow mucus in the posterior oropharynx. Repeated GAS rapid testing as well as serum Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus serologies were within normal limits. A multipathogen throat culture and specific cultures for gonorrhea and chlamydia were sent to the laboratory. Thayer-Martin culture grew gram-negative diplococci consistent with *Neisseria gonorrhoeae*. On repeated sexual history the patient disclosed having unprotected receptive oral sex with a 15-year-old male partner 4 weeks earlier. She received appropriate treatment with ceftriaxone and azithromycin and experienced a full recovery.

The Condition

Neisseria gonorrhoeae is a gram-negative diplococci more commonly known to cause cervicitis in females and urethritis in males as well as disseminated disease in both sexes characterized by fever, arthritis, tenosynovitis, and dermatitis. *Neisseria gonorrhoeae* is a rare (1%–2%) (1)(2) cause of pharyngitis that should be considered in a patient with pharyngitis after receptive oral sex. Changes in sexual practices and age of sexual debut are likely to make this diagnosis increasing relevant to frontline pediatric providers.

Most patients with pharyngeal *N gonorrhoeae* are asymptomatic. In fact, in the sentinel study of pharyngeal gonococcal infection conducted in a very high-risk population, pharyngeal *N gonorrhoeae* was not significantly more prevalent in those with sore throat compared with asymptomatic peers. (3) These data raise the question of whether *N gonorrhoeae* is pathologic or simply an incidental finding in patients with pharyngitis of a different etiology. Our patient's presentation and improvement with appropriate treatment suggest that it is in fact pathologic; however, additional research is needed to clarify the relationship between *N gonorrhoeae* and sore throat. Based primarily on case reports, when symptomatic, the clinical presentation of *N gonorrhoeae* pharyngitis varies widely, ranging from acute suppurative tonsillitis, to subacute mild pharyngitis, often with adenopathy, and usually without fever. (3)(4)(5)

Diagnosis

Given the variability in clinical presentation, suspicion based on symptoms alone is difficult, and epidemiologic clues should be used. The practice of receptive oral sex is the method of infection. Historically, rates are highest in men who have sex with men, followed by females, and lowest in men who do not have sex with men. (3)(6)(7) In addition, patients with urogenital gonorrhea are at increased risk for concurrent pharyngeal infection. (7) The percentage of youth reporting to have had sexual intercourse is decreasing. (8) However, younger birth cohorts are more likely to report oral sex during adolescence, indicating that the rate of oral sex during adolescence is rising. (9)

Risk stratification is limited by the ability to accurately ascertain sexual practices. Studies have found that patients underreport oral sexual exposures to health-care providers. (10) In addition, a minority of adolescent patients (20%) consider oral-genital contact to be sex and, therefore, many may not disclose such practices when asked generally about sexual history. (11) This was the case for this patient and likely contributed to her delay in diagnosis. Therefore, relevant sexual exposures should be explicitly discussed.

Standard throat culture will not identify *N gonorrhoeae*. When gonococcal pharyngitis is suspected, clinicians should contact their laboratory such that specific testing can be pursued. Traditionally, culture on Thayer-Martin medium has been used to diagnose gonococcal pharyngitis. However, nucleic acid amplification testing is more sensitive than culture on Thayer-Martin medium (95% versus 47%), with similar specificity (98% versus 100%). (12)

Treatment

Pharyngeal gonococcus is more likely to fail therapy than urogenital disease. Decreased antibiotic penetrance into the pharynx and horizontal gene transfer of resistance genes from commensal oral *Neisseria* species have been proposed as possible explanations. (13) The Centers for Disease Control and Prevention (CDC) recommends single doses of intramuscular ceftriaxone (250 mg) and oral azithromycin (1 g) for treatment of gonococcal pharyngitis. (14) Azithromycin serves to prevent the emergence of cephalosporin-resistant *N gonorrhoeae* and to treat possible *Chlamydia trachomatis* coinfection. (14)

Lessons for the Clinician

- *Neisseria gonorrhoeae* is a rare but not insignificant cause of pharyngitis.

- Clinicians should consider the diagnosis in high-risk populations or cases of pharyngitis in which other common causes have been excluded.
- Diagnosis can be made by nucleic acid amplification testing of a pharyngeal swab.
- Recommended treatment is 1 dose of intramuscular ceftriaxone (250 mg) and 1 dose of oral azithromycin (1 g).

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4 Diffuse Rash in a 2-month-old Girl

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AUTHOR DISCLOSURE Drs Dean, Geraghty, and Real have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A former 32-week-gestation, now 8-week-old girl presents to her primary care clinic with a diffuse rash. The rash started at 4 weeks of age as a single lesion on her right thigh. The rash subsequently spread throughout her lower extremities. The mother brought the patient to the clinic at 6 weeks of age for the rash, which had crusted over. The patient was diagnosed as having bullous impetigo and was prescribed oral cephalexin and topical mupirocin. A wound culture from that visit grew normal skin flora. Her rash continued to worsen. The patient presents today for her 2-month well-child check with persistent rash.

On physical examination, the patient's vital signs are within normal limits. Her rash is most prominent on the trunk and lower extremities. The rash appears as scattered, well-defined erythematous papules and pustules with overlying scale and several erythematous nodules. It involves the palms and soles and spares the diaper region (Fig 1). Other than the rash, she is doing well, with no fevers, fussiness, lethargy, or abnormal movements. She is growing appropriately and meeting her developmental milestones. Her mother denies anyone else at home with a rash. Of note, her mother's prenatal infectious laboratory test results were negative, including syphilis.

Preliminary laboratory evaluation reveals a negative treponemal immunoglobulin G/M, a negative human immunodeficiency virus antigen/antibody

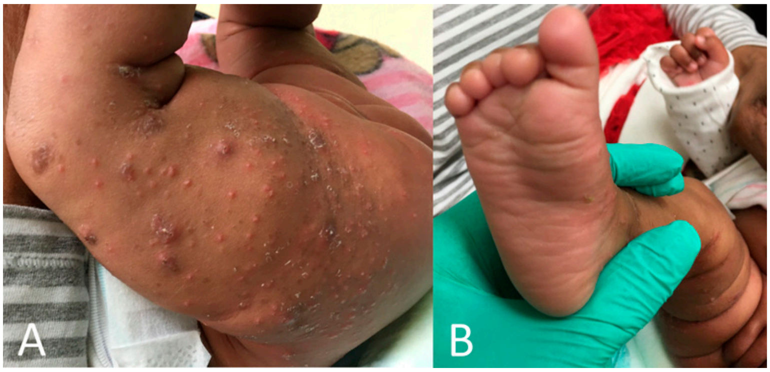

Figure 1. A. Erythematous papules, pustules, and nodules with overlying scale. Rash is most prominent on the lower extremities, with the diaper region spared. B. Crusted lesion on the plantar surface of the right foot.

screen, and a normal complete blood cell count. A telephone call with her mother the following day helps make the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/214.

DISCUSSION

While discussing the reassuring laboratory results, the patient's mother disclosed that although no one else at home currently had a rash, the family had an outbreak of scabies 3 months earlier for which the patient's 6 siblings and parents were all appropriately treated. Our patient was prescribed permethrin 5%. At a follow-up examination 1 week later, her rash was dramatically improved (Fig 2).

The Condition

Scabies is a parasitic skin infection caused by the *Sarcoptes scabiei* mite, common in overcrowded living situations. Mites can live both on and off the human host, including in clothing, bedding, furniture, and carpeting. It classically presents with a pruritic, papular rash involving interdigital webs on the hands, the flexor surface of the wrists, the extensor surface of the elbows, the abdomen, the axilla, and the genitalia. The rash is secondary to inflammatory and hypersensitivity reactions to the mite. The presence of burrows, serpiginous lines that are formed from the breakdown of mite digestive products, can be pathognomonic for this diagnosis. (1)

Neonatal scabies often has a markedly different presentation than scabies in older children or adults. It typically presents with diffuse vesicles, papules, and pustules; lacks burrows; and does not involve the interdigital web spaces. In addition, scabies in neonates rarely presents with obvious pruritus due to the patient's age. It has a similar presentation to other disease processes, which can lead to a delay in diagnosis or misdiagnosis altogether. (2) The differential diagnosis includes impetigo, folliculitis, congenital infections including syphilis and herpes simplex virus, papular urticaria, infantile acropustulosis, eczema, and Langerhans cell histiocytosis. (1)(2)(3)(4)

Congenital syphilis was a concern in this case owing to the location and appearance of the rash. Newborns with congenital syphilis are usually asymptomatic at birth and begin showing signs by 5 weeks of age. The first sign is typically rhinitis ("snuffles"), followed by a diffuse, desquamating maculopapular rash involving the palms and soles. Syphilitic pemphigus is a common finding that is manifested by a vesiculobullous rash that crusts over after 1 to 3 weeks and can mimic neonatal scabies. (5)(6)(7) A key differentiating factor is rash distribution, with congenital syphilis often including the diaper region and neonatal scabies often sparing it.

Diagnosis

Neonatal scabies can be diagnosed using a variety of methods. Most commonly, it is a clinical diagnosis that requires a high index of suspicion. Close contacts diagnosed as having scabies or with severe pruritus often aid in making the diagnosis. The gold standard for diagnosis is direct visualization of the scabies mite or eggs, which can be done via potassium hydroxide scraping of a burrow (if present) or skin biopsy. (1)(8)

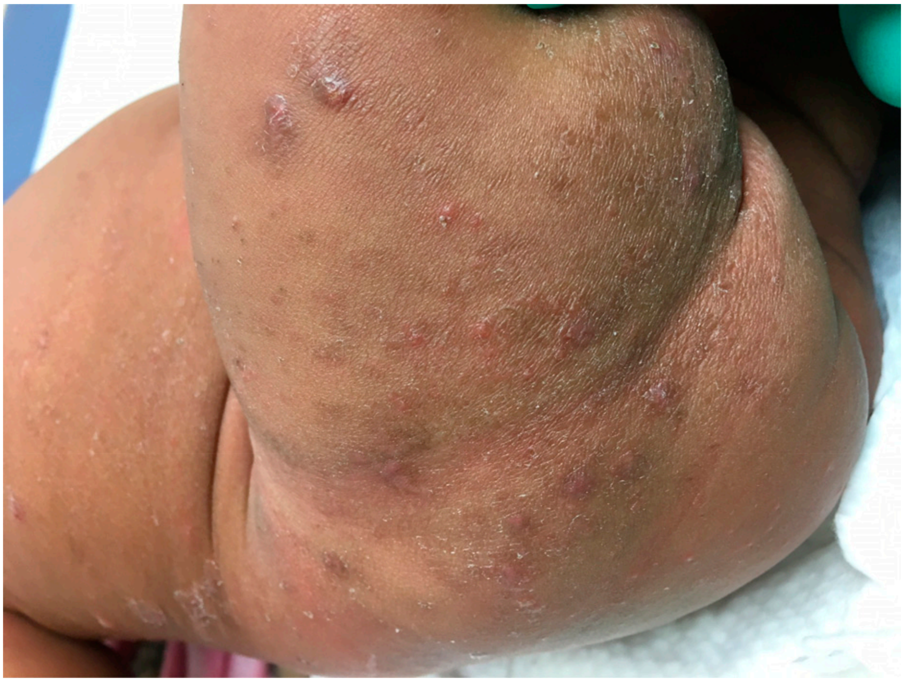

Figure 2. Appearance of the rash at follow-up 1 week after treatment with permethrin 5%.

Complications

A diagnosis of scabies can cause significant psychological and emotional distress for families, which should be addressed by providers. (1) The most common serious complication from scabies is a secondary bacterial infection, often caused by group A *Streptococcus* (GAS) or *Staphylococcus aureus*. Secondary infections caused by GAS have led to outbreaks of glomerulonephritis and rheumatic heart disease. (1)(4)(8) Postscabies pruritus, which can last for weeks to months, is another common complication. It is the result of a hypersensitivity reaction that can lead to excoriations causing dyspigmentation. Postscabies nodules are similarly caused by a hypersensitivity reaction and can persist for weeks. Families should be counseled and reassured about these common complications because they are often misinterpreted as reinfestation. (1)(2)(8)

Management

The standard treatment for scabies in adults and children aged 2 months and older is permethrin 5% cream applied once at bedtime for 8 hours, with an additional application as needed 1 week later. (1)(2)(8) A recent Cochrane review confirmed permethrin 5% as the most effective topical treatment for scabies. (8) Serious adverse effects to permethrin 5% are extremely rare. (1)

For children younger than 2 months, the recommended treatment is 10% topical sulfur in petroleum. (2)(4) However, this product must be compounded and can be difficult for some families to access. Due to the minimal risks associated with its use, some providers choose to use permethrin 5% in children younger than 2 months. (2) There are additional topical and oral treatment options for scabies that are generally less preferred due to inferior efficacy and significantly worse adverse effect profiles compared with permethrin 5%. (8) To prevent recurrence, all family members should be treated with at least 1 application of permethrin 5%. In addition, all bedding, clothing, and towels should be washed in hot water, and furniture and carpeting should be vacuumed. (1)(2)(8)

Lessons for the Clinician

- Neonatal scabies is characterized by diffuse vesicles, papules, and pustules and, unlike scabies in older children and adults, often lacks burrows or involvement of the interdigital web spaces.
- Neonatal scabies often spares the diaper region, which can differentiate it from the rash associated with congenital syphilis.
- Mites can live both on and off the human host, including in clothing, bedding, furniture, and carpeting, necessitating inquiry about remote infestations when scabies is on the differential diagnosis.
- In children aged 2 months and older, permethrin 5% is the most effective topical treatment for scabies.

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5 Ulcerated, Painful Genital and Perianal Rash in a 1-year-old Girl

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AUTHOR DISCLOSURE Drs Chagalamarri and Das have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 1-year-old previously healthy white girl presents to the emergency department with worsening genital and perianal rash. The rash started on her perineum 5 days before presentation and spread quickly to her pudental cleft. Her mother applied an over-the-counter diaper rash ointment with no relief. The toddler is playful but becomes fussy during diaper changes. She had a runny nose and 2 episodes of watery diarrhea in the past week. She has had no vomiting; a decrease in urine output; no oral, ocular, or nasal mucosal involvement; and no vaginal discharge. The older sibling had a red painful blister under her nose 2 weeks ago. The infant has a normal birth history, and her medical history is significant for atopic dermatitis. She has worn the same brand of diapers since her birth. Both her mother and sister help change her diapers at home.

Physical examination reveals a nontoxic-appearing infant with a temperature of 101°F (38.3°C). Other vital signs are within normal parameters. She has diffusely dry skin. Examination of the diaper area reveals multiple punched out

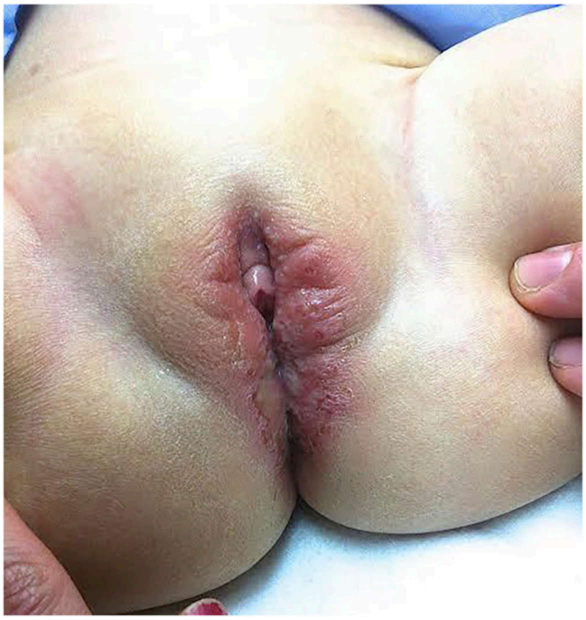

Figure 1. Ulcerated genital rash.

ulcerated lesions measuring 1.5 cm wide with erythematous bases and tiny blisters with serous fluid in the genital and perianal regions (Fig 1). The rash is foul smelling and tender to palpation. There is no lymphadenopathy.

Laboratory evaluation reveals the complete blood cell count and serum electrolyte levels to be within the reference range. Cultures of the blood and lesions are sent to the laboratory. The Gram-stain is negative. The culture and direct fluorescent antibody (DFA) results confirm our diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/216.

DISCUSSION

The patient's DFA test result was reported to be positive for herpes simplex virus (HSV) 1 in 24 hours, and her HSV culture results came back positive in 3 days. The tests confirmed our suspicion of a primary herpes infection based on the history of a sibling with a recent cold sore that had frequent physical contact with the child. The patient also had atopic dermatitis diffusely and scratched herself, which may have led to breaks in the skin and provided opportunity for inoculation. The child abuse medical team was consulted on this patient. After a thorough investigation of the family and of the evidence, they concluded that there had not been any evidence of abuse given the probable route of transmission from the sibling and the infant having no current or past injuries. She was treated with a 10-day course of oral acyclovir.

Differential Diagnosis

Diaper dermatitis is a common skin condition in infants and is usually caused by irritation from excessive moisture, yeast infection, or an allergic reaction to substances such as diaper dyes. Other possible diagnoses for rashes in the diaper region include seborrhea, atopic dermatitis, impetigo, scabies, psoriasis, and infections with cytomegalovirus, herpes virus, pinworm, and varicella virus. Seborrhea causes greasy patches of scaly skin in the inguinal region and is often found in other areas as well. Atopic dermatitis rarely occurs in the diaper region because the diaper tends to trap moisture in. Impetigo can develop when there is a break in the skin and can appear as tiny raised yellow fluid-filled vesicles and honey-colored crusted lesions. An autoimmune process such as psoriasis can present as reddened patches primarily in the diaper region without the distinctive silver scale and can cause concern for nonaccidental trauma. Other systemic autoimmune processes to consider when evaluating perianal ulceration are conditions such as Kawasaki disease and Crohn disease. Scabies can present in the diaper region with a widespread red, raised, itchy rash where the mites have burrowed in the skin, and it often affects multiple family members at the same time. Jaquet dermatitis is a severe form of contact diaper dermatitis that presents as pruritic nodules and ulcers in the genitalia of children with chronic diarrhea and incontinence and can be difficult to treat.

The Condition

After the neonatal period, infants usually acquire HSV (1 or 2) from direct skin-to-skin contact with someone with an active lesion, either a caregiver or from abuse. Most primary HSV infections during the period of childhood are asymptomatic, and shedding can occur in saliva without clinical disease. In childhood, gingivostomatitis is the most common presentation of HSV and can be accompanied by the characteristic painful ulcerative or clustered oral and perioral vesicles on an erythematous base, fever, irritability, poor appetite, and adenopathy. Primary herpes is usually more severe than recurrent herpes. Blisters or ulcers can occur on any part of the body, and autoinoculation can happen anywhere. Children often contract herpetic whitlow by autoinoculation from finger sucking when they have orofacial herpetic infection. Children with eczema are more prone to acquiring herpes due to breaks in the skin. Eczema herpeticum is a rare but severe infection that occurs when HSV vesicles become concentrated at the sites of skin damage usually in patients with atopic dermatitis. Rarely, HSV can lead to Stevens-Johnson syndrome. The incubation period of HSV is usually 2 days to 2 weeks, and the sores of a primary infection last 1 to 3 weeks.

Diagnosis and Treatment

Gram-stain and culture can identify secondary bacterial infections. Potassium hydroxide testing of scrapings from the rash can identity a fungal infection. To diagnose HSV, viral testing is standard. The vesicle must be unroofed, and the lesion's base must be swabbed. The sensitivity of viral culture is low and declines rapidly as lesions crust and heal. Polymerase chain reaction assays for HSV DNA are more sensitive than cultures. The DFA staining of vesicular scraping is a rapid diagnostic test to accompany viral culture but is less sensitive than viral culture.

Treatment is primarily supportive. Despite painful oral lesions, children should be encouraged to drink fluids to prevent dehydration. In immunocompetent patients, there are limited data available on the efficacy of antiviral agents on the course of primary mucocutaneous HSV infection. However, our patient was treated with an antiviral agent in an attempt to decrease the duration of her symptoms. Exposed lesions can be covered with a dressing to prevent infection risk to others. Oral HSV infection is common in children, and they should not be prevented from attending school. Contact with newborns or those with eczema or immunosuppression should be avoided until the sores are healed. The prognosis is good, with lesions healing in 2 to 4 weeks.

Lessons for the Clinician

- Infants and toddlers usually acquire herpes simplex virus (HSV) from direct contact with someone with an active lesion.
- Treatment with antiviral agents is typically not warranted in immunocompetent hosts who acquire primary mucocutaneous HSV.
- Children who are not sufficiently mature to engage in consensual sexual activity who present with genital HSV

warrant a multidisciplinary child protection investigation to assess for sexual assault.

Suggested Readings

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6

17-year-old Girl with a Skin Reaction from a Home Remedy

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PRESENTATION

A 17-year-old previously healthy girl with no chronic medical conditions presents to the clinic with a rash on her face. Three days before presentation, she awoke with the painful red rash. The day before onset she had pruritus of her chin without any other signs or symptoms and no other changes to the skin per her report. She has no history of eczema or allergies. She uses foundation for makeup and has not changed brands in more than a year. She notes no changes in soap or skin care products. There is no new exposure to detergents, plants, latex, nickel, or jewelry. No family members have similar skin lesions. She has not applied any other creams/lotions to the rash. Over the next 2 days the rash became more erythematous and painful but less pruritic. On presentation to the clinic the rash is erythematous and patchlike, with central ulcerations, well-demarcated borders, and overlying healing bullae along the chin and lower face (Fig). Vitals are all within normal limits. No other rashes are present on physical examination, and there are no other abnormal findings on examination.

On further questioning, a probable diagnosis emerges.

AUTHOR DISCLOSURE Drs Fick, Keshavaram, and McLaughlin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

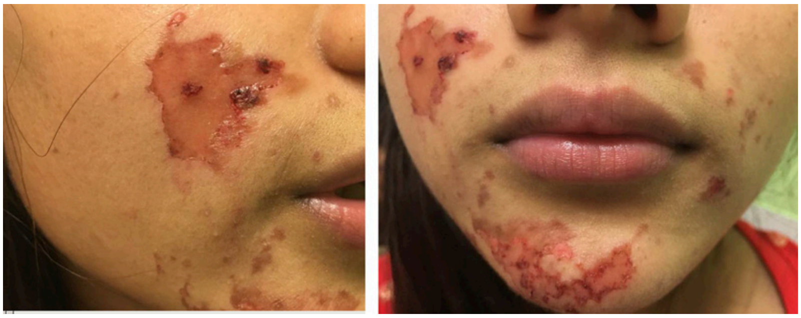

Figure. Clinical images of the chin and face with the described rash on presentation to our clinic, obtained via secure methods.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/4/218.

DISCUSSION

The patient admits that she performed an Internet search for home remedies to treat pruritus. She followed a recommendation to apply garlic, ground into a paste, to her face. No other chemicals or components were added to the mixture. She applied the paste in the evening and left it on overnight and awoke with the previously described rash.

This case highlights 2 important lessons: first is the importance of understanding the rare but possible chemical burn–like reaction that can be induced by garlic components and second is the importance of developing open lines of communication and a strong rapport with our adolescent patients to reduce the risk of harmful treatment strategies arising from seemingly benign "natural" home remedies.

The Condition

Garlic is a member of the Alliaceae plant family and has long been used in alternative medicine strategies as well as for culinary purposes. (1)(2) Some studies have shown benefit in adjunctive topical garlic application, when the garlic is extracted and prepared into a solution, for dermatologic conditions such as tinea infection or alopecia areata. (3)(4) Adverse effects of garlic ingestion may include nausea, vomiting, diarrhea, bronchospasm, anaphylaxis, hypoglycemia, and dermatitis, the latter of which can be seen with topical application. (5)(6)(7) The oxidative by-products in garlic have been known in some instances to cause a type IV hypersensitivity contact dermatitis and to involve the epidermis alone. (1)(8) Reports of acute chemical burn reactions are even more rare in the literature, (9)(10)(11)(12)(13)(14) and the cases that are reported often have a history of occlusive dressing application over the garlic paste. (15) In vitro studies have shown that allicin, the oxidative derivative of diallyl disulfide in garlic, is able to induce acantholysis to cause the chemical burn reaction. (16) The present case shows that the less common chemical burn occurrence is possible even without occlusive dressings. Risk of scarring when involvement occurs into the dermis is considered in these cases, and the location and cosmetic/psychological implications are taken into consideration as well.

Management

The concern for dermal involvement and the thin epidermis of the face made for challenging treatment in this patient. She was referred to the burn clinic given the concern for dermal involvement, and there she was prescribed topical antibiotic cream for 6 weeks, consistent with recommended guidelines. She was seen by psychology and occupational therapy while in the burn clinic and has been continuing with routine occupational therapy visits to prevent contractures. She was referred to dermatology for follow-up care and has been gradually improving. Current problems include postinflammatory hyperpigmentation and scarring from the dermal involvement of her burn, and she is working with dermatology for an optimal long-term cosmetic outcome. Often, if contact dermatitis is a concern, patch testing may be performed to assess for a hypersensitivity reaction. Patch testing was not performed in this patient because the pattern and sequence of her burns in addition to the lack of previous exposure to topical garlic paste was believed, on review of the literature, to be more consistent with acute chemical burn rather than contact dermatitis.

Implications

In addition to informing about a rare adverse effect of topical garlic application, this case also raises awareness of the importance of establishing clear, available, and open lines of communication between physicians and patients. An Internet search performed with the terms *itch of face treatment* returned 493,000 results, and 2 of the top 25 hits suggested garlic paste as one of the treatment options. With the ease of access to information via the Internet and the prevalent use of technology in younger generations, it is critical that practices attempt to grow in parallel with their patients. Clinicians may not be the first or only source of health-care information that our patients use. In addition, the growing number of Internet health resources makes it all the more important that our patients are aware of appropriate and inappropriate resources and the differences between the two. The problem is complicated further in that some remedies, as previously stated, are, in fact, based on supportive data, and trying to delineate when to use a given remedy can become quite challenging for the general public. This is a great opportunity for the pediatrician to provide sound recommendations. The ideal setting is likely one in which patients and parents seek to ask their physician questions regarding symptoms and management rather than an Internet search and before application of compounds that can potentially cause chemical burns. Several resources are available for providers and patients/parents to help facilitate these lines of communication, such as the Natural Medicines Comprehensive Database, the Medicine and the Media initiative from the American Academy of Pediatrics, and others. (17) This case shows a setting where adolescent-specific strategies as well as developing a strong rapport are especially critical.

Lessons for the Clinician

- Garlic can cause a variety of adverse effects, including nausea, vomiting, diarrhea, bronchospasm, anaphylaxis, and hypoglycemia. In addition, contact dermatitis and chemical burns have been seen in cases of topical garlic application.

- Contact dermatitis is seen more often than chemical burn with garlic application, but it is possible and should be kept in mind with cases of topical garlic application.
- Management of acute chemical burn from garlic application may include topical antibiotic cream and referral to a specialty clinic. Involvement into the dermis, scarring, and associated sequelae should be considered.
- Adequate lines of communication and appropriate use of technology and Internet resources with our patients should be kept in mind as the trend of technology use continues to evolve. Discussing these points and having open communication should questions arise will be important for pediatricians going forward.

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in Brief

Toxic Ingestions: Initial Management

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AUTHOR DISCLOSURE Drs Mangus and Canares have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Toxic ingestions represent a small but potentially life-threatening category of pediatric concerns. The peak age group for a toxic ingestion is 1 to 2 years, although the distribution in the pediatric population is bimodal, with a second peak in adolescence. Because toddlers tend to explore with their mouths, they are especially susceptible to unintentional ingestions of inappropriately stored household substances or medications. In contrast, adolescents may willfully ingest substances in an attempt to achieve a high or cause self-harm. Intentional ingestions are disproportionately more likely to have serious outcomes, including death. Therefore, all pediatricians should be familiar with the initial steps in assessment and treatment of potentially toxic ingestions.

Parents or health-care providers encountering a child with a known or suspected ingestion should always contact the Poison Control Center (PCC). This 24-hour hotline (1-800-222-1222) is staffed by toxicologists who provide expert medical advice to parents regarding whether the ingestion necessitates immediate medical assessment. The PCC will also assist physicians in the initial evaluation and management of an ingestion and provide recommendations about appropriate disposition. Note that the PCC hotline routes the call to the nearest center based on the telephone's area code, so calls made from mobile phones with long-distance area codes will be routed to the corresponding region's PCC.

The physician's first steps in management must include a rapid assessment of the ABCDs (airway, breathing, circulation, and disability/decontamination) and vital signs. Heart rate and blood pressure are not only essential in assessing the patient's overall clinical status and stability but may also provide clues to an unidentified ingestant. Depressed respiratory effort requires respiratory support and possibly intubation. Blood pressure should be monitored closely and fluid administered promptly in the case of hypotension. For the patient with profoundly depressed mental status, a point-of-care glucose determination and an empirical dose of naloxone are recommended. Finally, in cases of topical exposures, consider the need for decontamination by removing the child's clothes and washing or irrigating all affected areas.

Once the ABCDs are assessed, the physician should proceed with a focused history and physical examination. The history should include an attempt to identify the substance(s) that the child might have consumed (including the dosage strength of the pills/liquid medications when applicable), amount and timing of the ingestion, and subsequent symptoms or complaints. Always consider the possibility of a coingestion because the clinical picture may be nebulous when several substances are taken simultaneously. Caregivers who contact the physician before arrival in the clinic or ED should be instructed to bring whatever substance(s) the child might have ingested as well as the chemical's bottle or container. If the family arrives without the possible

Poisoning in the United States: 2012 Emergency Medicine Report of the National Poison Data System. Dart RC, Bronstein AC, Spyker DA, et al. *Ann Emerg Med.* 2015;65(4):416–422

Deadly Pediatric Poisons: Nine Common Agents that Kill at Low Doses. Michael JB, Sztajnkrycer MD. *Emerg Med Clin North Am.* 2004;22(4):1019–1050

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intoxicants, request that they contact someone “on the scene” to text a photograph of the product or bottle. When a container is available for inspection, the amount ingested can be estimated by noting how much is missing. Next, the physician should examine the patient purposefully, focusing on vital signs, neurologic and mental status, mucous membranes, pupils, and skin. Certain clinical examination findings may suggest specific toxidromes and aid in diagnosis when the ingested substance is unknown (Table 1).

Immediate steps in management include placing the patient on a cardiac monitor, establishing intravenous access, and collecting blood samples for laboratory tests, including a point-of-care blood glucose level. In most cases, obtaining acetaminophen, salicylate, and ethanol levels; a urine toxicology screen; and a complete metabolic panel is appropriate. These laboratory values can detect ingestions for which there is a known antidote (eg, *N*-acetylcysteine for acetaminophen) and identify treatable abnormalities (eg, hypoglycemia in β-blocker ingestions). Obtain a serum osmolarity and/or blood gas level if there is concern for ingestion of toxic alcohols (eg, methanol, ethanol) or substances causing acidosis (eg, salicylates). An electrocardiogram should be obtained to establish a baseline and screen for rhythm disturbances or conduction delays (such as QT prolongation), which may require immediate intervention.

Subsequent steps in management most often involve supportive care and close observation. Reexamine the patient frequently to assess for new or evolving symptoms. Correct blood glucose and serum electrolyte levels as indicated, and maintain hydration with intravenous fluids. Special attention should be given to urine output as a measure of hydration but also as a clue to an anticholinergic ingestion with urinary retention or to altered mental status with incontinence. If the patient is highly anxious or agitated, a weight-based dose of a benzodiazepine may be considered. It is imperative to recognize the subset of ingestions for which antidotes can be lifesaving (Table 2). Administer antidotes as early as possible and in consultation with a toxicologist.

In addition, the physician should carefully consider administration of activated charcoal, which minimizes absorption of drugs in the gastrointestinal tract by adsorbing the substance to the fine pores of the charcoal. Activated charcoal is prepared as an aqueous solution by mixing charcoal powder with sufficient tap water (eg, 30 g of charcoal in 240 mL of water). A single pediatric dose is 0.5 to 1 g/kg, up to 25 to 100 g. Activated charcoal is most effective when administered within the first hour after the ingestion and is ineffective for some substances (Table 3). Repeated doses may be indicated in large-quantity, highly toxic, or delayed-release ingestions. Of note, activated charcoal is contraindicated in patients with depressed mental status or risk of aspiration. If aspirated, charcoal may cause respiratory distress and chemical pneumonitis. For this reason, charcoal should only be administered orally in cooperative patients with normal mental status. Administration by nasogastric or

TABLE 1. **Toxidromes**

TOXIDROME	HR/BP	RR	TEMPERATURE	NEUROLOGIC/MENTAL STATUS	PUPILS	SKIN	OTHER
Anticholinergic (antihistamines, atropine)	↑	—	↑	Agitated, delirium Hallucinations	Large Sluggish	Dry, flushed	Urinary retention
Cholinergic (organophosphates)	↓	↑	—	Lethargy, seizures, coma, weakness	Small	Diaphoretic	Diarrhea, emesis, salivation
Opiates (morphine, heroin)	↓	↓	↓	Euphoria, somnolence, coma	Pinpoint	—	—
Sedative/hypnotic (benzodiazepine, EtOH)	↓	↓	↓	Confused, somnolent, coma	—	—	—
Sympathomimetic (cocaine, amphetamine)	↑	—	↑	Agitation, paranoia, hyperactivity	Large, reactive	Diaphoretic	—

BP=blood pressure, EtOH= ethyl alcohol, HR=heart rate, RR=respiratory rate.

TABLE 2. Toxic Ingestions and Antidotes

TOXIC INGESTION	ANTIDOTE
Acetaminophen	*N*-acetylcysteine
Anticholinergics	Physostigmine
Anticholinesterases	Atropine
Organophosphates	Atropine or pralidoxime chloride
Benzodiazepines	Flumazenil
β-blockers	Glucagon
Calcium channel blockers	Calcium
Cyanide	Amyl nitrite
Iron	Deferoxamine
Methanol/ethylene glycol	Fomepizole
Opioids	Naloxone
Tricyclic antidepressants	Sodium bicarbonate
Warfarin	Vitamin K

orogastric tube may be considered in select patients, so long as their airway is secured and protected.

Toxic ingestions represent an important clinical problem in the pediatric population. Whether an ingestion is suspected or confirmed, the physician should consult the PCC immediately and recontact the toxicologist as questions arise or the patient's status changes. Although pediatricians play a significant role in the management of toxic ingestions, the importance of parental education and guidance on prevention cannot be overstated. Primary care physicians should discuss safe storage of medications and household chemicals using the principles of "Up, High, and Out of Sight" and should instruct parents to have quick and easy access to the PCC hotline number. Caregivers can also be encouraged to download the mobile app *webPoisonControl*, an online tool that helps determine whether an ingestion is dangerous and requires medical attention. When an ingestion is suspected despite preventive measures, the astute physician should have a high index of suspicion, perform a focused history and physical examination, and contact the PCC promptly to successfully manage a possible ingestion.

TABLE 3. Substances Not Adsorbed by Activated Charcoal

SUBSTANCE	EXAMPLES
Heavy metals	Lead, iron, lithium, etc
Corrosives	Acidic and alkaline substances
Hydrocarbons	Kerosene, gasoline, etc
Alcohols	Acetone, ethanol, methanol, etc
Inorganic ions	Sodium, potassium, fluoride, etc
Pesticides	Organophosphates, etc

COMMENT: Yes, the importance of prevention cannot be overstated—it is truly the first step in the management of poisonings, and public health initiatives have been a fundamental support to our individual efforts. From the 1970 Poison Prevention Packaging Act to the 1971 Lead-Based Paint Poisoning Prevention Act to the 2016 Child Nicotine Poisoning Prevention Act, regulatory measures have played a major role in improving the safety of our children. However, in an environment where *regulation* has become a dirty word, with the federal guidelines protecting the integrity of our water and our air actively being dismantled, more and more the burden of promoting prevention will fall to us in our offices. With facts put into question and science put on the defensive, virtually every pediatrician has already been confronted with the rise of vaccine refusal, having to devote precious time to what should not be an issue. Unfortunately, we can likely expect more of the same, but we can take comfort at least in knowing that time devoted to prevention is well spent.

– Henry M. Adam, MD
Associate Editor, *In Brief*

in Brief

Brucellosis

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AUTHOR DISCLOSURE Drs Harrison and Posada have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Brucellosis is one of the most frequently encountered zoonotic diseases, with approximately 500,000 cases identified annually worldwide. *Brucella* are small, gram-negative, nonmotile, non–spore-forming, aerobic coccobacilli that can reproduce intracellularly only. Historically, human disease was thought to be caused by several different species, including *Brucella melitensis, Brucella abortus, Brucella suis,* and *Brucella canis.* However, these are now thought to be closely related organisms in a single species. The bacteria can survive for many days to weeks in dairy products but are killed by boiling, pasteurization, and souring or lactic acid fermentation of milk.

Brucellosis was first described in 1859 by British Royal Army Medical Corps (BRAMC) physician J.A. Marston among troops in Malta during the Crimean war. In 1886, David Bruce, another BRAMC physician, isolated the bacteria, later named for him, from the spleen of an affected patient in Malta. Approximately 10 years later, a Danish veterinarian, Bernhard Bang, isolated *Brucella* species (*B abortus*) from cattle with contagious abortions.

Disease is most commonly acquired from contaminated, unpasteurized sheep, cow, goat, and camel milk, and less frequently from direct contact with infected animals among farmers, veterinarians, and abattoir workers. Brucellosis is found worldwide but especially in developing countries, with the highest incidence in the Mediterranean basin, Arabian Peninsula, Indian subcontinent, Mexico, and South and Central America. The illness has also reemerged in Eastern Europe since the collapse of the Soviet Union. Historically, human brucellosis was found in the United States, but rates have declined with the eradication of bovine brucellosis by cattle immunization programs and test-and-slaughter techniques. Currently, in the United States there are fewer than 0.5 cases per 100,000 people, with the highest concentration of cases found along the US-Mexico border.

Brucella can be transmitted via inhalation, and this route has been the cause of laboratory-associated outbreaks, making it essential to inform the clinical microbiology laboratory whenever brucellosis is suspected. For safety reasons, serologic diagnosis is preferred at the local laboratory level, and if bacterial culture is to be performed, appropriate biosafety level 3 precautions need to be followed. Human-to-human transmission is rare, but congenital, sexual, and human milk transmissions have all been reported. Although once considered uncommon in younger age groups, disease is now more frequently recognized in children; they are at particular risk given their diet rich in milk (especially when unpasteurized) and in settings where animals share human living spaces.

Organisms enter the host via ingestion or inhalation or through mucous membranes or nonintact skin. The organisms are then taken up by polymorphonuclear cells or macrophages, where they can survive and replicate, evading the immune system. They are then transported to local lymph nodes, where bacterial replication continues, before spreading to reticuloendothelial organs, including the liver, spleen, and bone marrow.

Update on Laboratory Diagnosis of Human Brucellosis. Araj GF. *Int J Antimicrob Agents.* 2010;36(suppl 1):S12–S17

Clinical Manifestations and Complications in 1028 Cases of Brucellosis: A Retrospective Evaluation and Review of the Literature. Buzgan T, Karahocagil MK, Irmak H, et al. *Int J Infect Dis.* 2010;14(6):e469–e478

Brucellosis. Young E. In: *Feigin and Cherry's Textbook of Pediatric Infectious Diseases.* 7th ed. Cherry JD, Demmler-Harrison G, Kaplan SL, Steinbach WJ, Hotez PJ, eds. Philadelphia, PA: Saunders Elsevier; 2014:1611–1615

Incubation of disease is typically 2 to 4 weeks but can be several months. Infection can remain subclinical or can result in an acute febrile illness, an insidious illness, or a chronic illness. The clinical picture is often marked by nonspecific symptoms, including fever, arthralgia, and fatigue. Fever often waxes and wanes, which is why the disease is also known as *undulant fever*. Young children can present with low energy, refusal to bear weight, or failure to thrive. In endemic areas, brucellosis can be the cause of fever of unknown origin.

Focal or localized infection complicates more than half of all cases, and almost any organ system can be involved:

- Osteoarticular infection occurs in 50% of cases of brucellosis. Children typically have large peripheral joint involvement, which can present similarly to other types of septic arthritis, and adults can present with sacroiliitis or spondylodiskitis. Osteomyelitis can also occur.
- Neurologic involvement occurs in 10% of patients. Direct central nervous system invasion is rare; more common are headache, inattention, and depression.
- Gastrointestinal involvement is frequent in children, with two-thirds of pediatric cases accompanied by nausea, vomiting, anorexia, weight loss, and abdominal pain.
- The liver is likely always involved in brucellosis, although liver transaminase levels can be normal or only mildly elevated. Granulomas and liver abscesses can also occur.
- Cardiovascular disease is rare but can present with a range of disease, including endocarditis, myocarditis, pericarditis, endarteritis, thrombophlebitis, or mycotic aneurysms. Endocarditis causes much of the morbidity associated with brucellosis.
- Orchitis or epididymitis complicates 2% to 20% of cases of brucellosis.
- Respiratory complications are relatively rare, found in only approximately 1% of cases, but can present as a range of disease from bronchitis and pneumonia to pulmonary granulomas, nodules, and abscesses. Nodular disease can be confused with pulmonary tuberculosis. Laboratory workers exposed to *Brucella* via the airborne route can develop pneumonia.
- Bone marrow suppression is commonly encountered. The spleen is also often involved, given its role in the reticuloendothelial system, and hypersplenism can exacerbate hematologic abnormalities.
- A range of cutaneous or mucosal lesions has been reported and may represent hypersensitivity response, immune complex deposition, or direct bacterial invasion.
- Ocular involvement is also encountered, most commonly as anterior uveitis or chorioretinitis.
- Of women affected with brucellosis during pregnancy, one-half to one-third develop complications, which include intrauterine infection, fetal death, spontaneous abortion, premature delivery, and low birthweight. Neonates born to mothers with brucellosis may have congenital infection and malformations. Maternal treatment can help improve outcomes.

As with other intracellular pathogens, cell-mediated immunity is important for controlling established infection. Antibodies play a limited role in fighting infection but are helpful for diagnosis. Immunoglobulin (Ig) M levels increase in the first week of infection, followed by increased IgG levels in the second week. High or rising antibody titers can help establish the diagnosis. After treatment, IgG and IgM levels decline, but IgG decreases more quickly and IgM can persist at low titers for months to years. Persistently elevated IgG and IgA levels beyond 6 months indicate chronic infection or relapse. However, serology should be interpreted with caution because negative test results cannot exclude a recent infection, and antibodies (particularly IgM) can persist after recovery. The IgG avidity test can be useful because high avidity suggests immune memory (indicating old infection) and low avidity suggests more recent infection. *B canis* is not detected on standard serologic testing because of differences in the antigens it presents.

The diagnosis of brucellosis can also be made by isolating the bacteria from blood, bone marrow, or tissue cultures provided that biosafety level 3 precautions are followed to protect laboratory personnel from infection. In vitro, *Brucella* have slow growth, so cultures should be monitored for up to 28 days. Newer continuously monitored blood culture systems can detect growth within 7 to 10 days. Polymerase chain reaction–based testing can provide a more rapid diagnosis and can detect bacteria within 10 days of inoculation.

Treatment of brucellosis demands a multidrug regimen because there is a high rate of relapse with monotherapy. In vitro, many drugs show activity against *Brucella* but clinically are less effective. The cornerstone of treatment for uncomplicated disease in adults and children older than 8 years is doxycycline, with the addition of an aminoglycoside (streptomycin or gentamicin) or rifampin. In younger children and pregnant women, for whom tetracyclines are contraindicated, trimethoprim-sulfamethoxazole can be used as an alternative, with the addition of rifampin. Treatment of uncomplicated disease is usually for 6 weeks. Neurobrucellosis and endocarditis typically require longer treatment courses of 4 to 6 months with doxycycline or trimethoprim-sulfamethoxazole plus rifampin. Unfortunately, relapses are common (5%–15% cases) and frequently result from poor compliance with a prolonged course of therapy, inappropriate antibiotic drugs, or inadequately treated focal infection. Primary drug resistance to tetracyclines and aminoglycosides has not occurred, so these medications can be used to treat relapsed disease.

COMMENT: I must admit I'd never heard, as far as I can remember, of David Bruce before reading this *In Brief* by Drs Harrison and Posada. His story, it turns out, is interesting on several counts. Born in Australia to Scottish parents, Bruce and his family returned to their homeland when he was a young child, and he eventually earned his medical degree at the University of Edinburgh. Early in his career he joined the BRAMC and was posted to Malta, where he led the investigatory commission that eventually identified the cause of a serious outbreak of fever among British soldiers stationed on the island: So-called Malta fever turned out to be an infection caused by a bacterium initially named *Micrococcus melitensis*, later renamed in honor of Bruce. Shortly afterward, Bruce was sent to South Africa, where he studied an outbreak of cattle disease that he determined to result from a trypanosome transmitted by the tsetse fly. African trypanosomiasis, of course, causes not only the animal disease known as nagana but also sleeping sickness in humans, and the protozoan agent is named *Trypanosoma brucei*.

To his credit, on another front, Bruce insisted that his wife, Mary, who assisted him in all his work as a microbiologist, share credit for his accomplishments, and her name appears as coauthor on many of his published papers. His name is 1 of 23 that decorate the façade of the London School of Hygiene & Tropical Medicine as a leading founder in public health.

– Henry M. Adam, MD
Associate Editor, *In Brief*

Correction

An error appeared in the print version of the January 2018 In Brief "Contiguous Gene Syndromes" (Pereira E, Marion R. *Pediatrics in Review*. 2018;39(1):46-49, DOI: 10.1542/pir.2016-0073). In the Table, the description of 22q11.2 deletion syndrome should include "hypocalcemia" instead of "hypercalcemia." The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

ANSWER KEY FOR APRIL 2018 PEDIATRICS IN REVIEW

Vitamin Excess and Deficiency: 1. A; 2. C; 3. B; 4. D; 5. D.

Atopic Dermatitis: 1. D; 2. D; 3. E; 4. C; 5. A.

Clinical Presentation, Evaluation, and Management of Neuroblastoma: 1. C; 2. E; 3. D; 4. C; 5. D.

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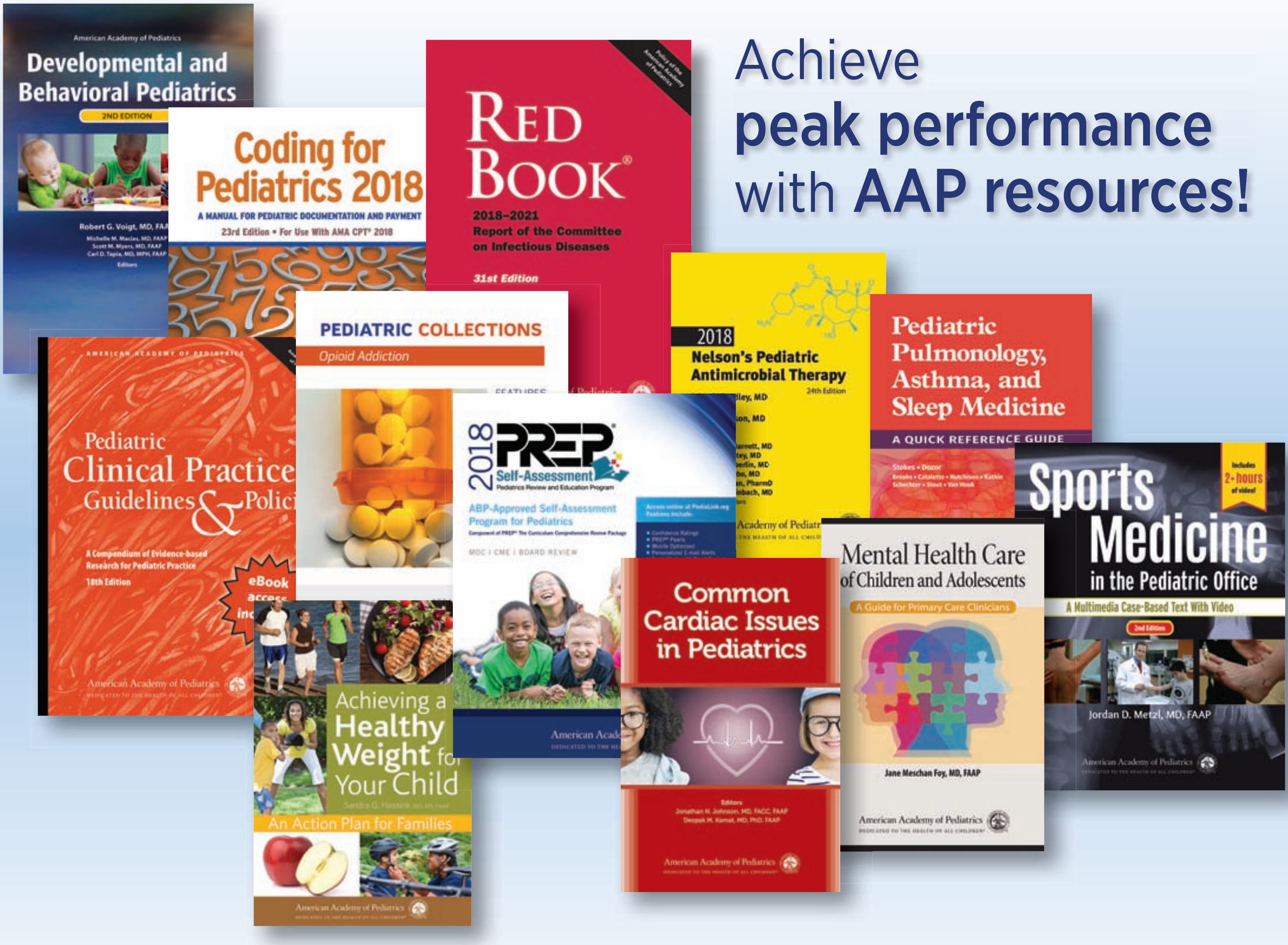

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Visual Diagnosis

7-year-old Girl with a Facial Rash

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PRESENTATION

A previously healthy, fully immunized 7-year-old girl presents to the dermatology clinic for evaluation of a rash on her left eyelid, forehead, and scalp. Her symptoms started 1 week earlier, first with pain of the left eyelid and subsequently, 2 days later, with scattered red papules around her left eye. She was evaluated by her pediatrician and treated with prednisolone for presumed allergic contact dermatitis to poison ivy. The rash evolved into vesicles distributed on the left eyelid and then spread to her forehead and scalp, prompting an emergency department visit. She was diagnosed as having cellulitis and was treated with oral clindamycin. Despite this therapy, she developed progressive edema of her left eyelid associated with eyelid pain. Her pediatrician urgently referred her to an ophthalmologist, who notes significant left periorbital edema but otherwise normal ophthalmic examination findings, including normal visual acuity and normal corneal examination without evidence of keratitis or ulceration. She is referred to a dermatologist on the same day, 9 days after her initial symptoms developed.

The patient has no fevers, nasal congestion, sore throat, cough, vomiting, diarrhea, headaches, or changes in mental status. The rash is associated with pruritus. She has not taken any new medications other than the antibiotics and corticosteroids prescribed for this eruption, and she has had no exposures to plants, new foods, or toxins. She has no known sick contacts. She has no significant medical history, and her immunizations are up to date.

On physical examination, she is well appearing but uncomfortable. She is unable to open her eye fully due to significant periorbital edema and associated discomfort. There is no conjunctival injection or discharge. There are numerous grouped vesicles, pustules, and crusted papules overlying an erythematous patch along the ophthalmic division of the trigeminal nerve, affecting the left upper eyelid, left forehead, and left scalp (Fig 1). There are no skin lesions at the tip or side of her nose to indicate nasociliary nerve involvement (negative Hutchinson sign). The rest of the examination results are normal.

DIAGNOSIS

A clinical diagnosis of herpes zoster (HZ) was made based on the acute onset of erythema and herpetiform vesiculopustules restricted to the ophthalmic (V1)

AUTHOR DISCLOSURE Drs Le, Jamison, and Kirkorian have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

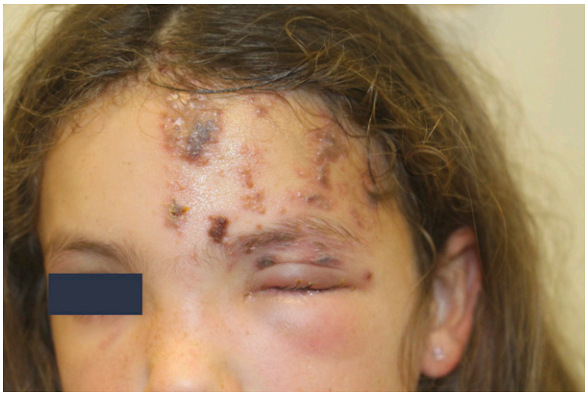
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Figure 1. A 7-year-old girl with erythematous grouped vesicles, pustules, and crusted papules affecting the left upper eyelid, left forehead, and left scalp with substantial left periorbital edema.

dermatome of the trigeminal nerve. The lack of involvement on the patient's nose suggested that there was no nasociliary nerve involvement, making ocular inflammation or corneal injury an unlikely complication. (1) To confirm the diagnosis, varicella zoster virus (VZV) polymerase chain reaction (PCR) was performed on fluid obtained from an intact vesicle. The sample was submitted to the Centers for Disease Control and Prevention (CDC) for specific evaluation for wild-type VZV versus vaccine-type VZV. The sample was positive for wild-type VZV, confirming the diagnosis of HZ. Herpes simplex virus (HSV) PCR and bacterial cultures were negative. Neither direct fluorescent antibody assay nor viral culture was performed because PCR is a more sensitive test and can distinguish wild-type versus vaccine-strain VZV. (1)

Discussion

Varicella zoster virus causes 2 distinct clinical presentations, including varicella (chicken pox) and HZ(shingles). The latter is an acute vesicular eruption characterized by the presence of erythema and grouped vesicles in a dermatomal distribution of 1 or more sensory nerves. Herpes zoster is caused by reactivation of a latent VZV infection in the sensory ganglia. (1)

In vaccinated children, HZ can occur due to reactivation of vaccine-related live attenuated varicella (Oka strain) or reactivation of wild-type virus. In our case, the patient's vesicular swabs were positive for wild-type VZV, implying that she either had a subclinical wild-type primary varicella infection before vaccination or had vaccine failure and acquired wild-type VZV after vaccination. Herpes zoster caused by wild-type VZV cannot be clinically distinguished from vaccine-strain VZV. A recent epidemiologic study found that patients with vaccine-strain HZ were more likely to have lumbar and cervical dermatomal involvement, whereas vaccinated and unvaccinated patients with wild-type HZ mostly had thoracic involvement. (2) Notably, the occurrence of HZ in a healthy child does not imply immunodeficiency. (3)

The accurate diagnosis of HZ can typically be made based on the distinctive clinical presentation, and laboratory tests are usually not necessary. (4) The differential diagnosis for grouped vesicles or pustules also includes herpes simplex virus infection, contact dermatitis, and impetigo. If testing is pursued, the diagnostic test of choice is a VZV PCR. (1) The PCR swabs may be sent to the CDC for delineation of wild-type or vaccine-related virus. This serves an important epidemiologic purpose by helping to determine whether the clinical course and outcomes of HZ from wild-type and Oka strain virus are similar and whether HZ is occurring more frequently in children in the era of varicella vaccination.

In children with HZ, the decision to treat with antiviral therapy depends on several factors, including patient characteristics that may increase the risk of severe infection, extent of infection, and timeline of infection. (1) In immunocompetent children, the presentation and clinical course is typically mild, with viral replication typically complete 72 hours after the rash develops. (1) Treatment with antiviral therapy within 24 hours after onset of rash in healthy, immunocompetent hosts results in only mild symptom reduction, and, thus, routine antiviral therapy is not necessarily recommended in otherwise healthy patients. (1) Antiviral treatment with oral antiviral medications should be considered in unvaccinated children older than 12 years, children with chronic cutaneous or pulmonary disease, and children treated with intermittent corticosteroids or salicylate therapy. (1) Intravenous acyclovir is recommended in patients at risk for severe VZV infection and disseminated zoster, including those with congenital T-lymphocyte defects or acquired immunodeficiency syndrome, chronic severe systemic disease, and patients receiving long-term corticosteroids or other long-term immunosuppressive therapy. (1) Prompt diagnosis is especially important in these high-risk patients because antiviral treatment within 24 hours of rash onset is optimal. (1) Delay in diagnosis in immunocompromised patients can result in rare, but serious complications, including meningoencephalitis, pneumonitis, hepatitis, or other disseminated visceral involvement. (5)(6) Postherpetic neuralgia is less common in children but can be a significant complication in those with ophthalmic HZ. (5) A delay in diagnosis of HZ involving the ophthalmic branch (V1) of the trigeminal nerve can result in keratitis and even permanent corneal scarring. (5) When HZ ophthalmicus is suspected, prompt referral to ophthalmology is critical. Antiviral

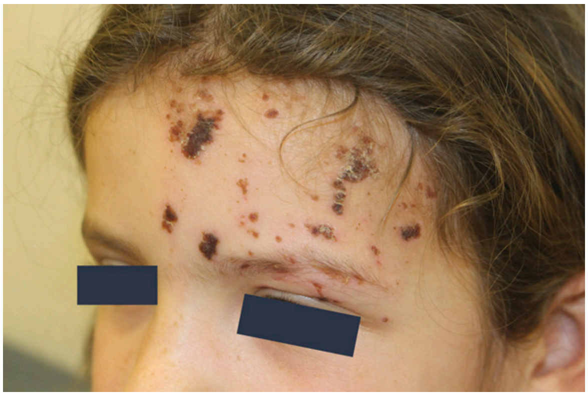
[redacted] [redacted]

Figure 2. A 7-year-old girl 1 week after initial presentation with crusting of all skin lesions and complete resolution of periorbital edema.

medications such as acyclovir, valacylcovir, or famciclovir are the preferred therapy and are most effective when started within 72 hours of symptom onset. Early initiation may reduce the risk of postherpetic neuralgia and result in a decreased incidence of keratitis and uveitis. (7) Although these severe complications are more likely to develop in immunocompromised children, they can rarely occur in the absence of immunodeficiency and in vaccinated children. (8)(9) Pediatricians should be familiar with the presentation of HZ and suspect this entity in a child presenting with an acute erythematous and vesicular eruption in a dermatomal distribution regardless of the patient's age, vaccination status, or lack of immunodeficiency.

Patient Course

Because the ophthalmic dermatome was involved, the patient was treated with acyclovir at the recommended dose of 80 mg/kg per day divided 4 times daily for a 7-day course. She returned to the clinic 1 week later and showed dramatic improvement, with crusting of all skin lesions and complete resolution of the periorbital edema, eyelid pain, and blurry vision (Fig 2). She experienced no neurologic, ophthalmic, or visceral sequelae from HZ.

Summary

- The diagnosis of herpes zoster (HZ) can be made clinically based on the characteristic presence of grouped vesicles on an erythematous base arranged in a dermatomal distribution of 1 or more sensory nerves.
- Laboratory testing is not needed for diagnosis, but if confirmation is pursued, the test of choice is varicella zoster virus polymerase chain reaction.
- Although HZ and its complications are more common in adults and immunocompromised patients, HZ can occur in immunocompetent and vaccinated children. In this population, HZ in usually self-limited and usually resolves without serious sequelae.

Suggested Readings

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Indication for BEXSERO

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

- BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO
- Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals
- Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope
- The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%)
- Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains
- Vaccination with BEXSERO may not result in protection in all vaccine recipients

Please see accompanying brief summary of full Prescribing Information for BEXSERO.

References: 1. Prescribing Information for BEXSERO. **2.** Prescribing Information for TRUMENBA.

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BRIEF SUMMARY

BEXSERO® (Meningococcal Group B Vaccine)
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The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO® is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. *[see Description (11) of full prescribing information]*

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of vaccine effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1) of full prescribing information].*

5.5 Altered Immunocompetence

Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In four clinical trials, 3058 individuals 10 through 25 years of age received at least one dose of BEXSERO, 1436 participants received only BEXSERO, 2089 received only placebo or a control vaccine, and 1622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in US and Poland, 120 participants 10 through 25 years of age received at least one dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by Menveo [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM$_{197}$ Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49% and 60% were White; 34% were Hispanic, 4% were Black,<1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) 11 through 17 years of age received at least one dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (UK), 974 university students 18 through 24 years of age received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1 dose of Menveo followed by 1 dose of placebo containing aluminum hydroxide (N=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (N=947). Across groups, median age was 20 years, males comprised 46%, and 88% were White, 5% were Asian, 2% were Black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were White, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, US/Poland, Canada/Australia, and in a subset of participants in the UK study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the US/Poland study, reports of unsolicited adverse events were collected up to one month after the second vaccination. Reports of all serious adverse events, medically attended adverse events and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), UK (12 months), US/Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants 10 through 25 years of age following each dose of BEXSERO administered 2 months apart or control in the US/Polish study[1] are presented in Table 1.

Table 1: Percentage of US and Polish Participants 10 through 25 Years of Age Reporting Solicited Local and Systemic Adverse Reactions within 7 Days after BEXSERO or Control, by Dose

Solicited Reaction[a]		**Dose 1**		**Dose 2[b]**	
		BEXSERO	**Placebo (Saline)**	**BEXSERO**	**Menveo**
		N=110-114	N= 94-96	N=107-109	N=90-92
Local Adverse Reactions					
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	> 50-100 mm	1	1	2	4
	> 100 mm	0	0	0	2
Systemic Adverse Reactions					
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

Clinicaltrials.gov Identifier NCT01272180.

[a] Erythema, and induration: Any (≥ 1 mm). Pain and systemic reactions: mild (transient with no limitation in normal daily activity); moderate (some limitation in normal daily activity); severe (unable to perform normal daily activity)

[b] Administered 2 months after Dose 1

Solicited adverse reaction rates were similar among participants 11 through 24 years of age who received BEXSERO in the other three clinical studies,[2,3,4] except for severe myalgia which was reported by 3-7% of subjects. Severe pain was reported by 8% of university students in the UK[3].

(continued on next page)

Non-serious Adverse Events

In the 3 controlled studies[1,2,3] (BEXSERO N=2221, control N=2204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) BEXSERO and 197 (9%) control recipients. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in BEXSERO recipients than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants 10 through 25 years of age who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO N=2716, Control N=2078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) BEXSERO recipients and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at two universities in the US, BEXSERO was administered as a 2 dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals 16 through 65 years of age who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one event considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

Adverse event reports received for BEXSERO marketed outside the US are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency, or to establish a causal relationship to vaccination. This list includes serious events or events which have suspected causal association to BEXSERO.

General disorders and administration site conditions:	Blisters at or around the injection site.
Immune System Disorders:	Allergic reactions (including anaphylactic reactions), rash, eye swelling.
Nervous System Disorders:	Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility in females or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Pregnancy Registry for BEXSERO

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to BEXSERO during pregnancy. Women who receive BEXSERO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years of age.

15 REFERENCES

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17 PATIENT COUNSELING INFORMATION

S*ee FDA-Approved Patient Labeling.*

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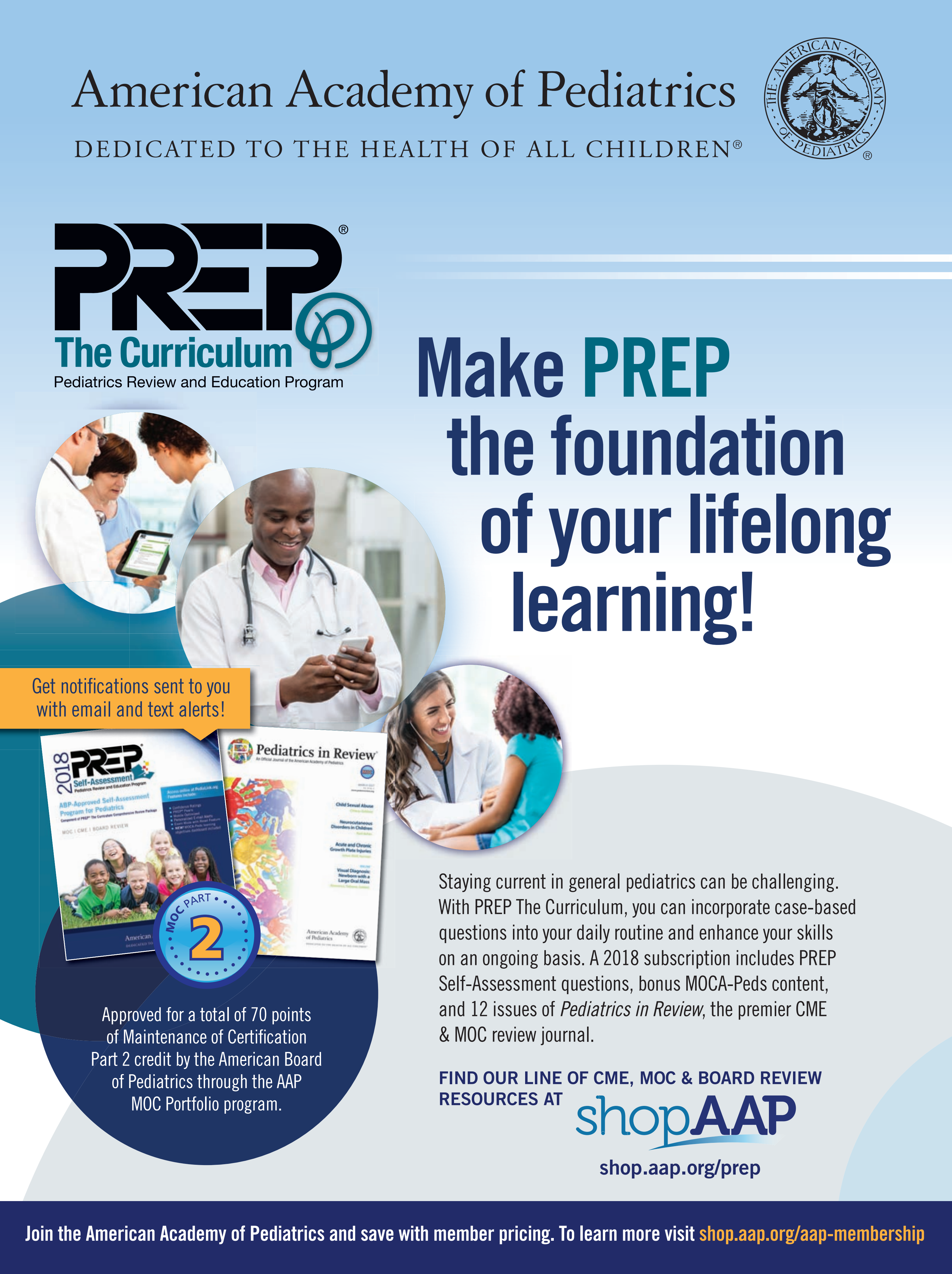

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Pediatric Vision Screening

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Practice Gap

Incorporating vision screening and a basic eye examination in the primary care setting can be challenging. Determining which screening examination to perform and when to refer a patient to a pediatric eye care provider is critical.

Objectives

After completing this article, readers should be able to:

1. Understand the importance of vision screening and know what conditions can be detected by periodic eye examinations.
2. Describe the components of a vision screening examination at different ages and plan an appropriate evaluation of vision.
3. Recognize the indications for referral to pediatric ophthalmology.

INTRODUCTION

Vision screening is crucial for early detection and prevention of vision loss in young children. Vision screening can be performed by primary care providers, trained laypersons (eg, school-based screenings), and eye care providers. Vision screening techniques are either provider-based (eg, traditional acuity testing, inspection, red reflex testing) or instrument-based. Instrument-based screening can often be performed at an earlier age than provider-based acuity testing and allows earlier screening for risk factors that are likely to lead to amblyopia and poor vision. The American Academy of Pediatrics (AAP) and the American Association for Pediatric Ophthalmology and Strabismus have developed guidelines to help practitioners screen for vision problems at different ages (Table 1).

THE IMPORTANCE OF VISION SCREENING

Vision screening allows the early detection of preventable vision-threatening or life-threatening conditions. Amblyopia, colloquially called “lazy eye,” is a reduction of best-corrected visual acuity that is not directly caused by any structural abnormality of the eye. It is caused by an abnormal visual experience resulting from strabismus, refractive error, or stimulus deprivation. Amblyopia occurs in 1% to 4% of children (1) and can be caused by visual deprivation (eg, cataract, ptosis, corneal opacity), strabismus (any form of eye misalignment, such as

AUTHOR DISCLOSURE Dr Loh has disclosed no financial relationships relevant to this article. Dr Chiang has disclosed that he has received research grants from the National Institutes of Health and the National Science Foundation, that he is an unpaid member of the Scientific Advisory Board of Clarity Medical Systems, and that he is a consultant/steering committee member of the RAINBOW study for Novartis. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. **Age-Appropriate Methods for Pediatric Vision Screening and Criteria for Referral**

		RECOMMENDED AGE				
METHOD	INDICATIONS FOR REFERRAL	NEWBORN–6 MO	6 MO UNTIL COOPERATIVE FOR VISION TESTING	3–4 Y	4–5 Y	EVERY 1–2 Y AFTER AGE 5 Y
Red reflex test	Absent, white, dull, asymmetrical	Evaluate at all ages				
External inspection	Structural anomaly (eg, ptosis, hemangioma)	Evaluate at all ages				
Pupil examination	Unequal size, poor reaction to light, irregular shape	Evaluate at all ages				
Corneal light reflex	Asymmetrical or displaced		*	*	*	*
Instrument-based screening	Failed to meet screening criteria		*	*	*	*
Cover test	Refixation movement			*	*	*
Visual acuity (distance, monocular)		Failure to fixate and follow	Failure to fixate and follow	20/50 or worse in either eye	20/40 or worse in either eye	20/30 or worse or 2-line difference between eyes

Asterisks indicate the method of vision screening that should be performed in that age column.

esotropia or exotropia), high refractive error (eg, hyperopia or myopia), or anisometropia (asymmetry of refractive error between the eyes). Amblyopia is more easily and successfully treated the earlier it is detected, and it becomes impossible to treat after 7 to 9 years of age. Patients and caregivers may be unaware of the consequences of delayed evaluation and treatment. (2) The short window of opportunity to save vision underscores the importance of vision screening to detect amblyopia or its risk factors while treatment is still effective. Vision screening assessments in early childhood reduce the risk of vision loss at age 7 years by more than 50%. (3)

Vision screening and eye examinations within the medical home create frequent and early opportunities to diagnose a myriad of conditions. In the first year of life, causes of deprivation amblyopia are more frequent and result in the most profound vision loss. Conditions affecting infants include corneal opacities, cataracts, ptosis, glaucoma, and retinoblastoma. Deprivation amblyopia in infancy can develop very rapidly. A few weeks of deprivation of visual stimulus in 1 eye from a dense cataract or complete ptosis can result in profound amblyopia that often requires years of numerous hours of patching treatment. Early detection of retinoblastoma can save the child's vision and life. Ocular abnormalities may be the first recognized sign of a systemic disease. For example, blurred vision and bilateral cataracts in a child can be the first presentation of a neurodegenerative disease, cerebrotendinous xanthomatosis, that if unrecognized causes irreversible cognitive impairment. Early recognition and treatment with an oral medication can prevent lifelong disability. In addition, a crossed eye may be the first sign of vision loss in a baby with optic nerve hypoplasia as part of septo-optic dysplasia. Effective screening by the pediatrician can lead to earlier diagnosis of systemic problems.

The etiologies of amblyopia vary with age. Form deprivation amblyopia is more frequent and profound in infants. A unilateral cataract in a newborn will cause substantial amblyopia if untreated and should be removed within weeks; in contrast, a traumatic cataract in a 6-year-old with previously good vision is much less likely to cause amblyopia, and in the absence of other damage from the trauma, the cataract can be removed nonurgently. In children younger than 3 years, strabismus is the most common cause of amblyopia; in children 3 to 6 years old, strabismus and anisometropia contribute equally. (4) In younger children (eg, up to age 3 years), the examination is more challenging and the disorders can be subtle, but early detection can have a profound effect on the child's vision and future if treatment is initiated quickly. To detect these abnormalities, vision screening should be performed by primary care providers or trained laypersons (eg, school-based screenings) throughout childhood. The combined sensitivity of a series of screening evaluations is higher than a single evaluation, especially if different methods are used for each screening evaluation. (5) Unfortunately, children present to the ophthalmologist at age 6 to 8 years for their first eye examination with significant amblyopia (frequently, anisometropic amblyopia) whose vision loss would have been preventable if they had been detected earlier and been prescribed glasses at a younger age. The routine assessment of vision in all children cannot be overemphasized; special attention should also be given to children with disabilities. Children with developmental delay can experience a delay in identification of their ocular disease that further impedes successful treatment.

Some children should be referred directly for a comprehensive examination. For example, poor eye contact by a term infant with the caretaker after 8 weeks of age warrants further assessment (8 weeks' adjusted age for premature children). Table 2 lists red flag signs and symptoms for possible eye problems. Special attention should be given to children with a history of a known medical risk factor for vision problems, including prematurity, cerebral palsy, craniofacial abnormalities, Down syndrome, Marfan syndrome, congenital cytomegalovirus, eyelid hemangiomas, Sturge-Weber syndrome, sickle cell disease, and nevus of Ota. Children with medical conditions such as diabetes or juvenile idiopathic arthritis should receive a comprehensive evaluation soon after diagnosis.

PROVIDER-BASED VISION SCREENING

Red Reflex Testing

The red reflex test is the most important screening test for infants and young children. Red reflex testing requires no patient participation and can be performed shortly after birth. A direct ophthalmoscope is used to view both eyes simultaneously from 2 to 3 ft away from the patient (Fig 1).

The red reflex represents reflection of the retina through a clear pupillary axis. Distortion in the red reflex can be caused by an abnormality anywhere in the visual axis (eg, in the retina [retinoblastoma], vitreous [vitreous hemorrhage], lens [cataract], or cornea [scar or infection]). A difference in the red reflex can also be caused by asymmetry in the refractive power of the eye, which can cause amblyopia and be vision threatening. The AAP recommends routine screening for structural abnormalities using red reflex testing. (6) Figure 2 represents examples of normal and abnormal red reflex testing.

Red reflex testing allows for the prompt diagnosis of and referral for leukocoria (white pupil), which occurs when there is an opacity preventing a clear view of the retina. The most concerning cause of leukocoria is retinoblastoma, a life-threatening tumor in children. All patients with abnormal red reflex tests should be referred to pediatric ophthalmology, and concern for leukocoria should be urgently referred.

External Examination

The external examination of the eyes, eyelids, and face is an important part of the visual system screening in a primary care office. A simple penlight examination of the eyelids can reveal ptosis, capillary hemangiomas, and port wine stains, which are risk factors for amblyopia and systemic diseases. Careful inspection of the globe size is important in screening for pediatric glaucoma, which can cause either unilateral or bilateral ocular enlargement. Ptosis requires prompt identification because it can cause amblyogenic astigmatism even if the lid itself does not block the visual axis. Substantial ptosis obstructing the visual axis requires urgent referral in any child. For subtler ptosis, referral to an ophthalmologist is appropriate for children too young to assess vision using either optotypes (figures or letters of different sizes used to test vision acuity) or instrument-based screening. In older children who pass a

TABLE 2. **Signs and Symptoms of Potential Vision Loss**

SIGN/SYMPTOM	POTENTIAL EYE PROBLEM	PEDIATRIC PROVIDER ACTION
No eye contact in an infant >8 wk old corrected age	Decreased vision, delayed vision maturation	Vision screen and refer to ophthalmologist
Head tilt or face turn	Strabismus, nystagmus, high astigmatism	Vision screen and refer to ophthalmologist
Unable to comply with vision screening	Decreased vision	Refer to ophthalmologist
Tearing	Congenital nasolacrimal duct obstruction, glaucoma	Age <1 y without other signs of glaucoma (enlarged corneas, photophobia, blepharospasm), vision screen Age >1 y refer to ophthalmology
Photophobia	Congenital glaucoma, inflammation	Vision screen and consider referral
Squinting	Refractive error, strabismus	Vision screen and consider referral

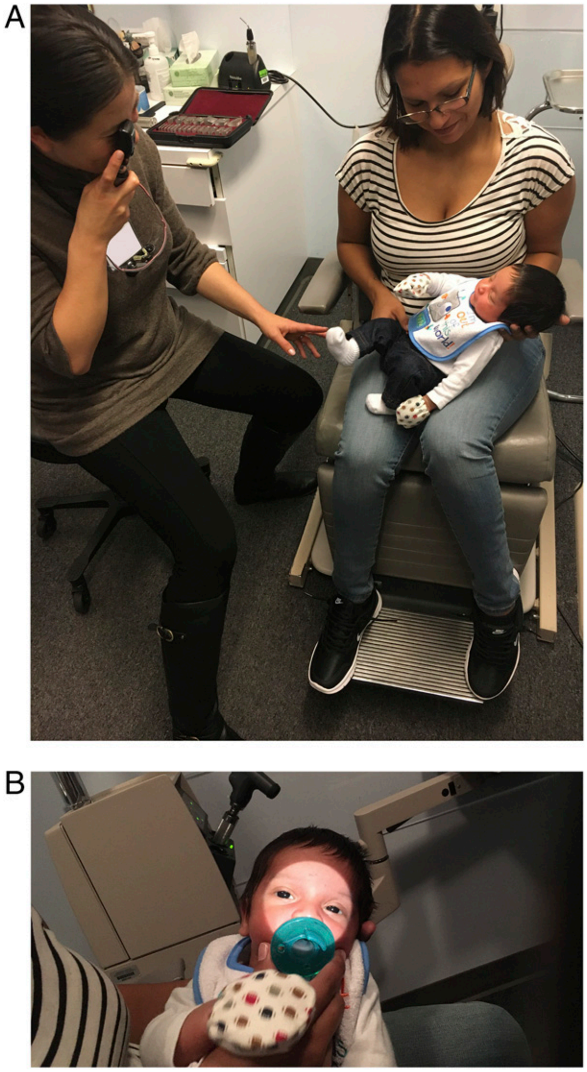

Figure 1. A. A provider performing red reflex testing approximately 2 to 3 ft from the infant. B. The provider's view of bilateral red reflex viewing both eyes simultaneously.

vision screening with subtle ptosis, referral to ophthalmology is not required. Ptosis combined with miosis, which is an asymmetrically constricted pupil, may represent Horner syndrome and would require an ophthalmology evaluation for neuroblastoma in children. In addition, an enlarged globe (buphthalmos) is caused by elevated eye pressure. Any enlarged eye, especially with a history of tearing and photophobia, should be referred immediately for concern of pediatric glaucoma. Careful inspection by an astute primary care provider is crucial to the early identification of vision-threatening and potentially life-threatening problems.

Visual Acuity Testing

What is normal visual acuity? Normal acuity changes with age because visual acuity improves as children grow. Infants,

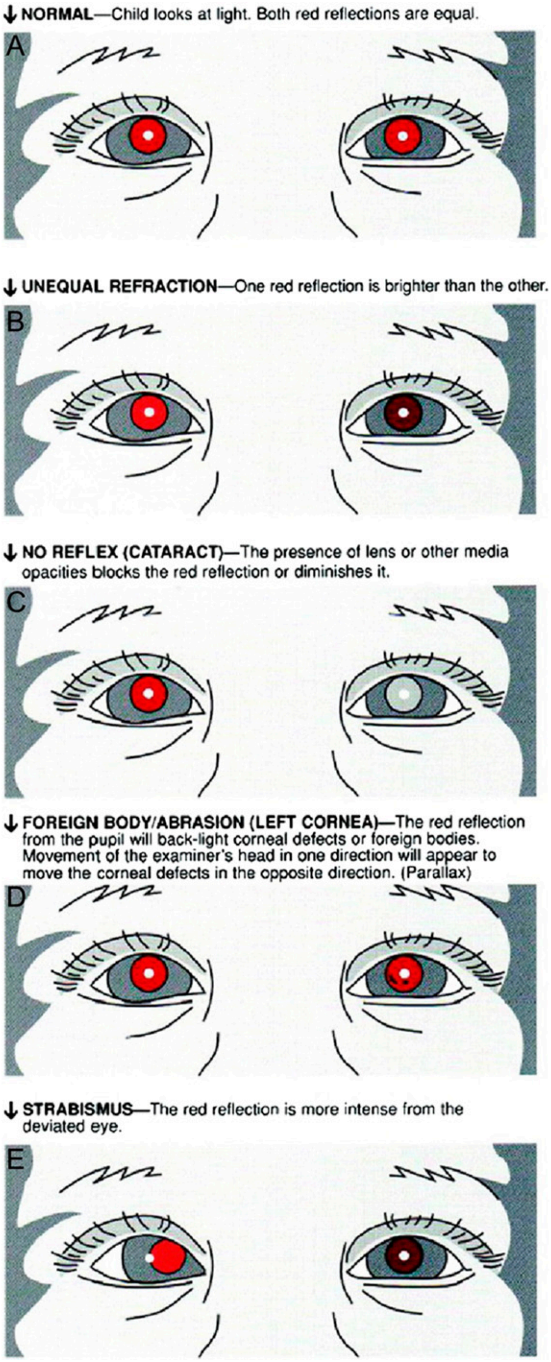
↓ NORMAL—Child looks at light. Both red reflections are equal.
A
↓ UNEQUAL REFRACTION—One red reflection is brighter than the other.
B
↓ NO REFLEX (CATARACT)—The presence of lens or other media opacities blocks the red reflection or diminishes it.
C
↓ FOREIGN BODY/ABRASION (LEFT CORNEA)—The red reflection from the pupil will back-light corneal defects or foreign bodies. Movement of the examiner's head in one direction will appear to move the corneal defects in the opposite direction. (Parallax)
D
↓ STRABISMUS—The red reflection is more intense from the deviated eye.
E

Figure 2. Red reflex examination. A. Normal: Child looks at light. Both red reflections are equal. B. Unequal refraction: One red reflection is brighter than the other. C. No reflex (cataract): The presence of lens or other media opacities blocks the red reflection or diminishes it. D. Foreign body/abrasion (left cornea): The red reflection from the pupil will backlight corneal defects or foreign bodies. Movement of the examiner's head in 1 direction will appear to move the corneal defects in the opposite direction. E. Strabismus: The corneal light reflex is temporally displaced in the misaligned right eye, indicating esotropia. (Reprinted with permission from American Academy of Pediatrics; Section on Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Academy of Ophthalmology; American Association of Certified Orthoptists. Red reflex examination in neonates, infants, and children. *Pediatrics*. 2008;122(6):1402. Image courtesy of Alfred G. Smith, MD © 1991.)

0 to 2 months of age, should blink in response to bright light and have equal pupillary responses. Additional signs of normal vision in infants include the "eye-popping reflex." For the first year of life, children with normal vision manifest an eye-popping reflex where the eyelids retract on turning off the lights. It can be clinically helpful to determine that an infant has at least light perception vision when parents are concerned that their baby cannot see. The eyelid retraction disappears when ambient light is turned on, and the phenomenon is thought to be a form of primitive startle reflex. (7) Fixation and tracking should improve and become reliable around 6 to 8 weeks of life. Premature children may have some delay in their visual development and may not fix and follow until their adjusted age reaches 8 weeks. Newborns may have intermittent strabismus (either eye turning outward or inward), but this should resolve by 2 to 4 months of age. Any constant strabismus is considered abnormal at any age, and intermittent strabismus after 4 months warrants referral. From age 6 months to 2 years, children should be able to fix and follow an object monocularly and have normal alignment. After age 3 to 5 years, subjective vision can usually be measured using eye charts. Video 1 demonstrates a technician checking vision in a 2.5-year-old girl using matching LEA SYMBOLS® (Good-Lite Co, Elgin, IL) optotypes (standard symbols such as letters or pictures). A practical tip for checking vision in very young children is to begin the "matching game" before covering each eye to confirm understanding and to encourage participation before introducing the eye patch.

Video 1. Video of a technician checking vision monocularly in a 2.5-year-old girl using matching LEA SYMBOLS® optotypes and an eye patch.

Children 3 years or older typically can participate in provider-based subjective visual acuity testing. Children who cannot participate in subjective visual acuity testing are considered untestable, and untestable children have been shown to have vision problems more often than testable children. (8) Repeated examination in 6 months is recommended, and inability to assess vision in a 3- to 5-year-old merits referral to an eye care provider. (5) Recommendations for referral based on visual acuity are presented in Table 1.

Recognition visual acuity testing is the gold standard in vision screening and the preferred method for assessing vision to detect amblyopia, especially in older children. Vision is routinely tested at 2 standard distances (10–20 ft for distance vision and 14–16 in for near vision). Vision should be measured monocularly, which involves sufficiently occluding 1 eye with an adhesive patch or occlusive tape. Vision should be checked while the child is wearing any necessary corrective lenses. Young children improve performance if allowed to match optotypes presented on the chart to a handheld card (eg, Video 1). The choice and presentation of optotypes on an eye chart affect the visual acuity obtained. The current recommendations by the American Academy of Ophthalmology are for LEA SYMBOLS® (Fig 3) or HOTV letters to be used as the preferred optotypes for preliterate children. The goal is for the optotypes to be standardized, clear, and without cultural bias. Allen figures, tumbling E charts, and Lighthouse symbols are not standardized and are no longer recommended as preferred optotypes.

Cover and Hirschberg Testing for Strabismus Evaluation

A common concern among parents is for strabismus (misalignment of the eyes). An esodeviation refers to a convergent misalignment of the visual axis. Esophoria is a latent esodeviation that under normal binocular conditions the eyes remain properly aligned. Esotropia is an esodeviation that is not controlled by fusional mechanisms, so the deviation is constantly manifest. Exodeviation is a divergent strabismus that can be latent (exophoria) or manifest (exotropia). Most people have some latent strabismus (esophoria and exophoria) that can be revealed by extensive cover testing and is not amblyogenic, but manifest strabismus is a frequent cause of amblyopia.

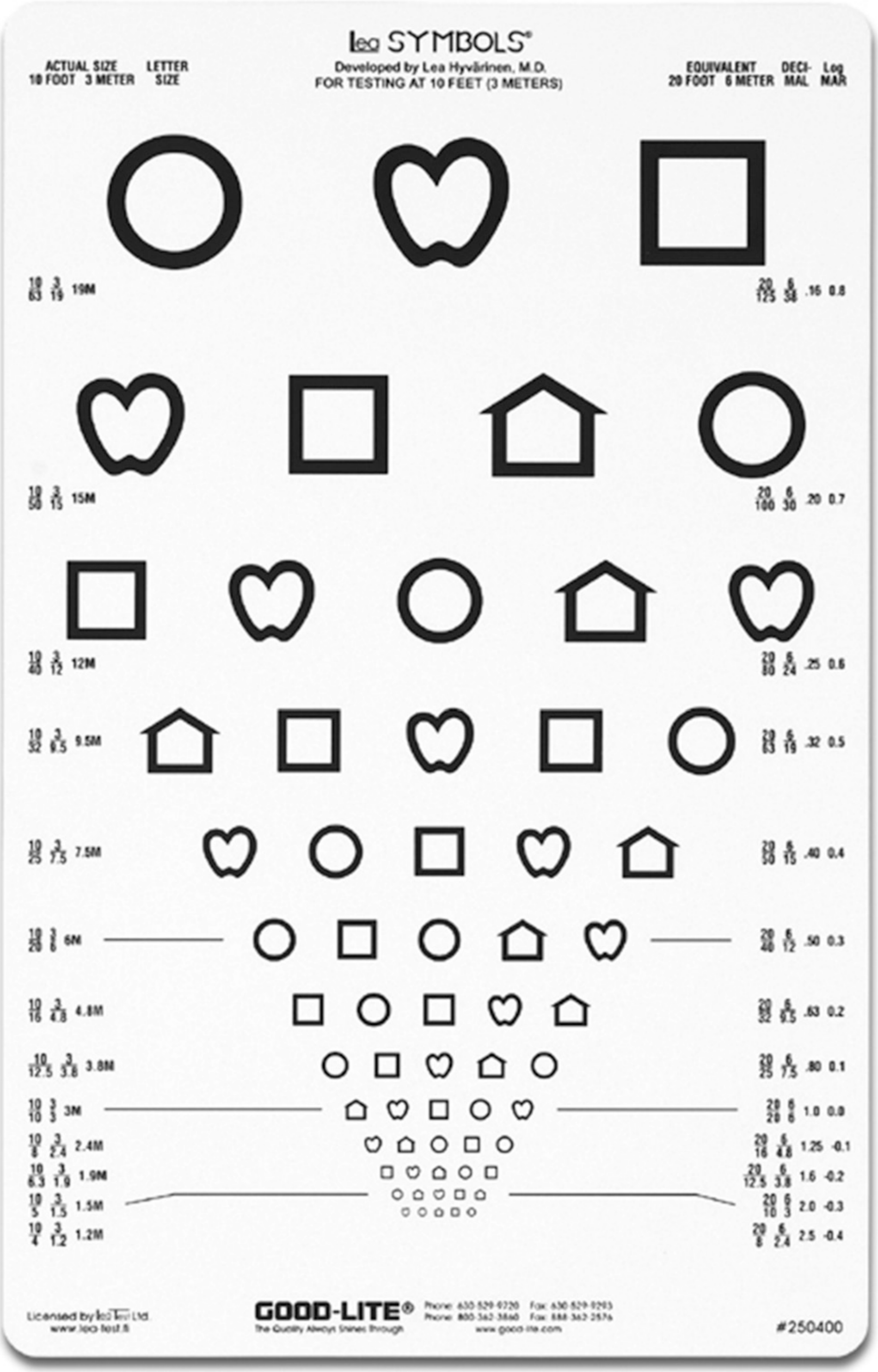

Figure 3. LEA SYMBOLS®. (Reprinted with permission from Good-Lite Co, Elgin, IL.)

Examination techniques such as cover testing and Hirschberg testing are crucial for evaluating concern for strabismus. For example, parents can report esotropia but may in fact be appreciating pseudoesotropia. Children with large epicanthal folds or a flat nasal bridge often have pseudoesotropia (appearance of crossed eyes when the eyes are in fact straight), which may be diagnosed by symmetry of the pupillary light reflex when shining a penlight toward the patient or by cover

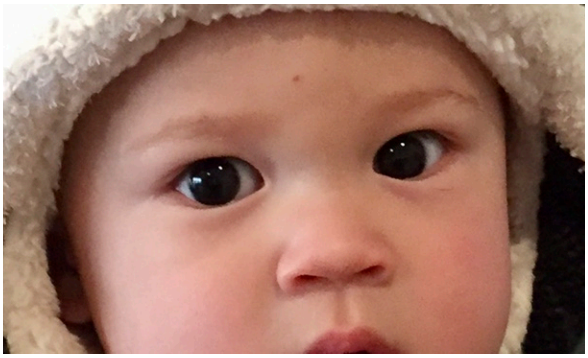

Figure 4. Pseudoesotropia with wide epicanthal folds. Despite the left eye appearing crossed because there is less white sclera visible nasally, the well-centered light reflexes confirm pseudoesotropia.

testing (Fig 4). If the primary care provider is confident in the diagnosis of pseudoesotropia, these patients do not require referral to ophthalmology.

The cover-uncover test and the Hirschberg test are used to determine whether there is a manifest misalignment of the eyes. The Hirschberg test is a simple test where a penlight is directed at the patient while he or she is looking straight ahead. The light reflex should be reflected in the center of each pupil if the patient's eyes are straight. If there is a manifest exotropia, the light reflex will be nasal to the pupil. If there is a manifest esotropia, the light reflex will be temporal to the pupil (Fig 5). The Hirschberg test, along with the cover test, can be very helpful in distinguishing a benign pseudoesotropia from a true manifest strabismus requiring ophthalmology referral.

The cover test requires the child to fixate either at near (eg, a sticker on an examiner's nose or a toy held up close) or distance (eg, a television or parent at the end of the room). If the patient is watching your nose and there is a manifest exodeviation of the right eye (ie, the right eye is turning out), the left eye is straight and fixating. The cover test involves covering the fixating eye and watching the deviated eye shift toward central fixation. If the misaligned eye is drifted out, the eye will shift inward when the fixating eye is covered. If the deviated eye is turned in, the eye will shift outward when the fixating eye is covered. Video 2 demonstrates a child with esotropia whose inward-turned eye refixates outward when his opposite eye is covered.

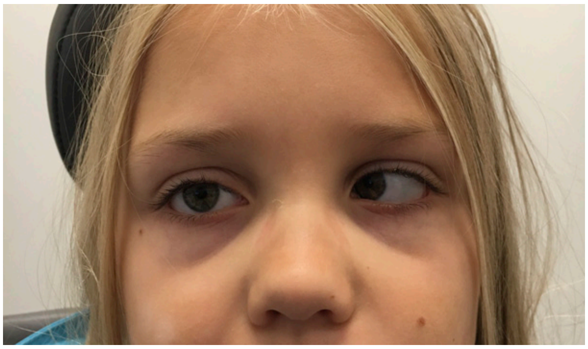

Figure 5. Esotropia of the left eye.

Ocular Motility and Nystagmus

In addition to alignment, ocular motility is an important part of the eye examination. Parents who observe "funny eye movements" may be the first observers of a complex strabismus syndrome, such as congenital fourth nerve palsy, Brown syndrome, or Duane syndrome. Congenital fourth nerve palsy is characterized by a vertical misalignment of the eyes caused by weakness of the ipsilateral superior oblique muscle. Children typically have a head tilt toward the side of the palsy. Brown syndrome is also characterized by vertical misalignment of the eyes caused by a deficit of the superior oblique muscle where the affected eye cannot elevate in adduction. Duane syndrome is characterized by anomalous innervation of the lateral rectus by the sixth cranial nerve causing limitation in horizontal eye movements as well as retraction of the globe on attempted adduction. If a patient has an esotropia, evaluating motility is important for determining the urgency of the referral. The most common forms of esotropia, including congenital esotropia and accommodative esotropia, typically have normal ocular motility. Limitation of abduction (eye movement away from the nose) can

Video 2. Video of a provider evaluating for strabismus. This is a 7-year-old boy with esotropia whose inward-turned eye refixates outward when his opposite eye is covered.

Video 3. Video of a technician using a vision screener with a 6-year-old boy.

be a sign of a sixth nerve palsy in contrast to congenital or accommodative esotropia with full ductions and no abduction limitation. In addition, the presence of nystagmus or unusual eye movements in an infant or young child can indicate decreased vision or neurologic dysfunction and warrants further evaluation by either an ophthalmologist or a neurologist.

Pupil Examination

The pupils should be equal in size and reactive to light from birth. A dim room and using a bright light elicits the best pupil response, especially in newborns. The pupils normally will decrease in diameter with accommodation and if the child is looking at the examiner at near; the pupil response may be less marked if the pupils are small already during

TABLE 3. Instrument-Based Vision Screening Devices (18)

	DEVICE				
	ISCREEN (14)	**PLUSOPTIX S09, S12C (19)**	**SPOT SCREENER (12)**	**RIGHTON RETINOMAX (4)**	**SURESIGHT (20)**
Type	Photoscreener	Hybrid	Hybrid	Autorefractor	Autorefractor
Monocular/binocular	Binocular	Binocular	Binocular	Monocular	Monocular
Image interpretation	Vendor	Automated	Automated	Automated	Automated
Conditions screened	Refractive error, strabismus, anisometropia, anisocoria, cataracts	Refractive error, strabismus, anisometropia, anisocoria	Refractive error, strabismus, anisometropia, anisocoria	Refractive error	Refractive error
Cost per machine, $	4,200	7,595	7,490	12,495	3,999
Cost per test	~$10	None	None	None	
Time per test, seconds	7	1	1	1	1
Time for results	<1 h	Instant	Instant	Instant	Instant

Data from Colburn J. Comparison of instrument-based vision screening devices. American Academy of Ophthalmology website. https://www.aao.org/pediatric-center-detail/vision-screening-performance-data-resource-2. Published 2014. Accessed August 1, 2017 accommodation. Any evidence of anisocoria or pupils of different shapes should be referred to an ophthalmologist.

INSTRUMENT-BASED VISION SCREENING

Provider-based visual acuity assessment depends on child participation and screener experience. With practice, instrument-based vision screening can be fast and require less participation from the child. (Video 3) Instrument-based screening can be very helpful in screening children before reliable subjective visual acuity can be obtained. (9) Recent guidelines released by the AAP in January 2016 recommend instrument-based screening starting at 1 year old and continuing until the child can reliably read the eye chart. (10)

There are 2 types of instrument-based vision screening: photoscreeners and autorefractors. Neither type measures visual acuity itself but rather measures risk factors for vision loss, including myopia, hyperopia, astigmatism, and strabismus. Children with retinal disease or structural causes for amblyopia may have false-negative screening tests. Amblyopia risk factors were identified in 5% of preschool children participating in 16 photoscreening programs of more than 400,000 children. (11) Approximately 4% of children younger than 6 years have myopia, 5% to 10% have astigmatism, and up to 20% have hyperopia. (12)(13)(14) Photoscreeners are binocular devices that estimate refractive error, media clarity, ocular alignment, and eyelid position. Photoscreeners have been shown to have high sensitivity and specificity when used in community and office settings. (15)(16)(17) Autorefractors monocularly estimate refractive error and are useful for screening for high refractive error and anisometropia. Once a child is old enough to reliably read an eye chart, direct visual acuity should supplement vision screening. Instrument-based vision screening would not detect structural abnormalities causing decreased vision (eg, retinal dystrophies or optic nerve hypoplasia) even if vision was poor because visual acuity is not directly measured. Table 3 compares common commercially available instrument-based vision screening devices.

VISION SCREENING CODING

Last, *Current Procedural Terminology* codes 99173 and 99174 are specific for provider-based visual acuity screening and instrument-based photoscreening, respectively. The AAP recommends that vision screening not be bundled into the global code of well-child care. Adequate reimbursement for photoscreening must be encouraged to promote widespread adoption of vision screening. Unfortunately, some insurance plans may not cover vision services. The National Eye Institute has information regarding vision services available to uninsured and underinsured children (https://nei.nih.gov/health/financialaid).

Summary

- On the basis of expert consensus as well as prospective cohort research, routine vision screening decreases the incidence of vision loss in early childhood. (3)
- Based on consensus, the most important aspects of a provider-based vision screening are red reflex testing, external examination of lids and adnexa, ocular motility, and visual acuity testing.
- Based on some research evidence as well as consensus, instrument-based vision screening can be used to reliably evaluate vision in children. (10)
- Referral to an eye care provider is indicated if a patient does not pass a component of the vision screen or when further diagnostic and management recommendations are required.

References for this article are at http://pedsinreview.aappublications.org/content/39/5/225.

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1. A 3-year-old boy is brought to the clinic for a routine health supervision visit. He was the product of a full-term pregnancy and spontaneous vaginal delivery. He has been followed in the same clinic for his health supervision visits and he has had normal growth and development. Which of the following is the recommended method to be used to best assess visual acuity in this child?
   - A. Allen figures.
   - B. Ishihara plates.
   - C. LEA SYMBOLS®.
   - D. Lighthouse symbols.
   - E. Tumbling E charts.
2. You are evaluating a 2-year-old boy with Down syndrome. His mother is concerned that his eyes are turning in. In view of the fact that patients with Down syndrome have epicanthal folds and a wide nasal bridge, you want to differentiate true strabismus from benign pseudoesotropia. Which of the following is the most appropriate next assessment to perform in this patient to determine whether this is a true finding?
   - A. Check for a symmetrical red reflex.
   - B. Check for buphthalmos.
   - C. Confirm normal visual acuity.
   - D. Demonstrate an "eye-popping reflex."
   - E. Perform the Hirschberg test.
3. A 6-year-old girl is found to have left exodeviation on physical examination using the Hirschberg test and the cover-uncover test. Which of the following responses to the cover-uncover test with near focus confirms the strabismus in this patient?
   - A. Cover the left eye and the right eye turns laterally.
   - B. Cover the left eye and the right eye turns medially.
   - C. Cover the right eye and the left eye does not change position.
   - D. Cover the right eye and the left eye turns laterally.
   - E. Cover the right eye and the left eye turns medially.
4. Your practice is considering the implementation of instrument-based vision screening in young children to comply with the 2016 American Academy of Pediatrics guidelines. Which of the following is the primary goal for this screening tool?
   - A. Identify retinal disorders.
   - B. Identify risk factors for vision loss.
   - C. Identify optic nerve hypoplasia.
   - D. Measure intraocular pressure.
   - E. Measure visual acuity.
5. The parents of a 9-month-old child are concerned about their child's vision because there is a strong family history of glaucoma. The child is brought to the office for vision screening and evaluation. The presence of which of the following findings would be most concerning for the diagnosis of glaucoma?
   - A. Anisocoria.
   - B. Photophobia.
   - C. Ptosis.
   - D. Squinting.
   - E. Strabismus.

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Screening for Poverty and Poverty-Related Social Determinants of Health

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Practice Gap

Pediatricians should screen for and address poverty and poverty-related social determinants of health because they have clear negative effects on children's health and well-being. This task requires coordination of services beyond the medical home. Pediatricians may also advocate at local and federal levels to further serve patients living in poverty.

Objectives

After completing this article, readers should be able to:

1. Define social determinants of health and understand their effect on children's health.
2. Access tools to screen for poverty and poverty-related social determinants of health.
3. Describe evidence-based interventions that address poverty and poverty-related social determinants of health.
4. Outline government policies and programs for impoverished families for which pediatricians may advocate.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
APA	Academic Pediatric Association
EITC	Earned Income Tax Credit
SNAP	Supplemental Nutrition Assistance Program
WIC	Special Supplemental Nutrition Program for Women, Infants, and Children

CASE SCENARIO

A 13-year-old girl has an appointment with her pediatrician for follow-up of her asthma. She had gone to the emergency department 3 times in the 10 days before the appointment for cough and difficulty breathing. Each time, she was given nebulizer treatments, improved, and was discharged home. She was also treated with oral corticosteroids and azithromycin. Her symptoms have persisted up to the day of the appointment. Her mother reports complete compliance with her inhaled medications, oral corticosteroids, and antibiotic. On further questioning, her mother reports that she, the patient, and the patient's younger brother are living in a shelter. The shelter apartment they initially lived in had no heat, so they were transferred to an apartment on a different floor. The heat did not work in the new apartment, so they were transferred to an apartment in another building, which did not have heat or hot water. The patient's mother tried using the stove to heat the apartment, but it had a strange *odor, so she turned it off, concerned that it would make the patient's asthma worse. The patient has missed 8 days of school during this period.*

BACKGROUND

Children are the poorest demographic of the US population. (1) In 2014, 43% of all US children younger than 18 years lived in "poor, near poor, or low-income" households, defined as household incomes up to 200% of the federal poverty level (annual income of $47,700 for a family of four for the 48 contiguous states, excluding Alaska and Hawaii, which have different federal poverty guidelines). (2) From a societal perspective, the cost of childhood poverty is estimated to be $500 billion a year, which is almost 4% of the gross domestic product. This cost is attributed to decreased productivity and greater social expenditures. For example, impoverished children are less likely to finish high school, which is associated with higher rates of unemployment and incarceration in adulthood and higher rates of teen pregnancy. Poverty is also associated with multiple adverse effects on children's health and development, including low birthweight, infant mortality, developmental delay, chronic illness, injury, malnutrition, obesity, and behavioral concerns. Furthermore, poverty makes parenting more challenging, as caregivers struggle to balance caring for their children with meeting their families' basic social needs. (3)

Given the known negative outcomes associated with poverty, it is important for pediatricians to identify families living in poverty. This need has been long recognized by the American Academy of Pediatrics (AAP) and the Academic Pediatric Association (APA), and in the spring of 2016, these 2 organizations independently issued statements addressing the growing problem of childhood poverty and its implications for children's health. The statements urge pediatricians to screen for poverty-related social determinants of health, to develop interventions to reduce the adverse effects of poverty, and to advocate for programs and policies aimed at eliminating childhood poverty. The AAP and APA recommend several programs that pediatricians may establish in their practices and encourage pediatricians to advocate for specific governmental policies addressing poverty. The statements highlight that pediatric providers are uniquely positioned to address childhood poverty through their common objective of preventing childhood diseases, through their opportunity to provide anticipatory guidance throughout children's lives, and through their shared passion for supporting children and families. (3)

The objectives of this article are 1) to review screening tools for poverty and poverty-related social determinants of health that pediatricians may use in practice; 2) to describe interventions that support patients whose screens are positive; and 3) to outline government policies and programs for families living in poverty for which pediatricians may advocate. As an example, we describe how we address each of these items in our urban academic general pediatric practice, located in one of the poorest communities in the United States.

RECOMMENDATIONS FOR SCREENING

The World Health Organization defines social determinants of health as "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life"(4). Social determinants fall under several domains, including income, food security, housing stability, academic attainment and literacy, legal status/immigration, and personal safety, and poverty has a unifying effect on many of them. (5)

The AAP recommends screening for social determinants of health at each health supervision visit from birth until age 21 years. New guidelines recently put forth in *Bright Futures*, a compilation of evidence-based pediatric preventive care guidelines, encourage providers to consider social factors, such as food insecurity and violence, that may affect a child's and family's health. (6)

Table 1 is a compilation of screening tools for social determinants of health that may be used in pediatric practices and may be particularly helpful to providers supporting families living in poverty. Included are general screening tools, which screen for multiple social determinants, as well as domain-specific screening tools. Screening for social determinants of health should be tailored to each community, addressing the most common issues faced by that community (food insecurity or housing instability) as well as issues that are less common but critical (abuse and neglect). Parent input can be exceedingly helpful in directing which issues to identify. Screening should be appropriate for a child's age and should be performed at multiple visits, as families' needs change over time. (7)

Multiple barriers to screening for poverty-related social determinants of health exist in clinical practice. Before screening, practices need to identify which social determinants are relevant to their patient population, choose which screening tools to use, decide who will administer them, and determine how often and at which ages to screen. Screening may require additional time, space, clinical staff, and expenses; may interrupt the workflow of the practice; and

TABLE 1. **Screening Tools**

SCREENING TOOL	DESCRIPTION	LANGUAGES	READING LEVEL	WEBSITE REFERENCES
Accountable Health Communities Core Health-Related Social Needs Screening Tool	• 10 questions (variable responses depending on social determinant) addressing housing instability, food insecurity, transportation needs, utilities, and interpersonal safety • Can be self-administered	English		https://nam.edu/wp-content/uploads/2017/05/Standardized-Screening-for-Health-Related-Social-Needs-in-Clinical-Settings.pdf The screening tool is embedded in the article posted at this website.
Food insecurity 2-question screening tool	• In the past 12 mo: a) We worried whether our food would run out before we got money to buy more b) The food that we bought just didn't last and we didn't have money to get more • If 1 or both statements are often or sometimes true, the screen is positive for food insecurity • Administered by clinician	Any language		http://www.hungercare.org/provider-resources/
Health Leads	• 13 items (yes/no) addressing parent education, parent employment, child care, housing instability, food insecurity, utilities, income assistance/public benefits, health insurance, legal assistance/immigration, home/neighborhood safety, and domestic violence • Can be self-administered	English and Spanish	4th grade	https://healthleadsusa.org/tools-item/health-leads-screening-toolkit/ The screening tool is part of the Social Needs Screening Toolkit that can be downloaded at no cost from this website.
HelpSteps	• Questions addressing nutrition and fitness (disordered eating, opportunity for physical activity), parent education, safety equipment (smoke detectors, car seats), heath-care access, housing instability, utilities, food insecurity, parent employment, income assistance, substance use, interpersonal violence • Can also request help with sexual health needs, special health-care needs (cognitive and physical disabilities), mental health needs, and parenting needs and support • Self-administered web-based tool that progresses through a series of questions about the above items and links patients to resources based on their responses • Specific to Massachusetts	English		https://www.helpsteps.com/home.html

Continued

TABLE 1. (Continued)

SCREENING TOOL	DESCRIPTION	LANGUAGES	READING LEVEL	WEBSITE REFERENCES
IHELLP (Income, Housing, Education, Legal Status, Literacy, Personal Safety)	• Variable number of questions (clinician-dependent, yes/no and open-ended) addressing: - **Income** (employment, food insecurity, utilities, health insurance, income assistance/ public benefits, transportation) - **Housing** (housing instability, crowding, lead exposure, smoke exposure, substance use) - **Education** (child education, school violence, child care) - **Legal** (legal assistance, immigration status) - **Literacy** (parent education, parent literacy, reading to children) - **Personal safety** (community and domestic violence, parent and child trauma exposure) • Administered by clinician	Any language	4th grade	https://www.aap.org/en-us/Documents/IHELLPPocketCard.pdf
SWYC (Survey of Well-Being of Young Children) Family Questions	• 9 questions (yes/no and 3- and 4-point Likert scale) addressing smoke exposure, substance use, food insecurity, parent depression, domestic violence • Part of larger screening tool assessing developmental milestones, behavioral/ emotional development, and family stress • Administered by clinician	English, Spanish, Portuguese, Burmese, and Nepali	6th grade	https://www.floatinghospital.org/The-Survey-of-Wellbeing-of-Young-Children/Overview.aspx
WE CARE (Well Child Care, Evaluation, Community Resources, Advocacy, Referral, Education)	• 6 questions (yes/no) addressing parent education, parent employment, child care, housing instability, food insecurity, and utilities • Can be self-administered	English and Spanish	3rd grade	http://pediatrics.aappublications.org/content/135/2/e296 The screening tool can be found in the supplement to the article posted at this website.
WellRx	• 11 questions (yes/no) addressing food insecurity, housing, utilities, income, employment, transportation, substance abuse, child care, safety, and abuse • Can be self-administered	English and Spanish	5th grade	http://www.jabfm.org/content/29/3/414/T1.expansion.html

may not be reimbursable. (3)(8) Families should be informed that screening is universal in the practice. (7) Once screening is implemented, practices may find that the needs of their patient population surpass their ability to provide services. Practices are, therefore, encouraged by the AAP and the APA to take small steps toward screening, to establish systems such that they are not overburdened by screening and by their patients' needs, and to take advantage of existing models of such systems. (3)(8)

Our Practice

We initially began screening for social determinants of health by using the IHELLP screening tool described in Table 1 to take an expanded social history at 1 of 3 academic practice sites in our network. The IHELLP screening tool was developed at Boston Medical Center and Boston Children's Hospital and is a mnemonic for **I**ncome, **H**ousing, **E**ducation, **L**iteracy, **L**egal status, and **P**ersonal safety, reminding providers to address multiple domains of poverty-related social determinants in the social history. (5) This tool led to improved detection of social needs in the inpatient setting when used as part of a multiple stepwise behavioral intervention at another academic institution and was modified to fit the needs of the outpatient pediatric population in our clinics. (9) We began by educating providers about the social determinants of health as they pertained to our patient population and informed them of local community and government-based resources. We created prompts in our electronic medical record for IHELLP that can be added to the social history section of a patient's medical record, and we developed lists of domain-specific resources that can be printed from our electronic medical record and given to patients at the end of the visit. This screening initiative was first implemented among residents in our Social Pediatrics Residency Program at 1 training site and was later expanded to include all pediatric residents at all 3 clinic sites.

Most recently, the ambulatory network sites at our institution have begun universal screening for social determinants of health using the Health Leads screening tool. Caregivers complete the paper-based screening tool before or during the visit with the clinician. The clinician reviews the results and places an appropriate referral for positive screens. Depending on the clinic site, a social worker and/or a community health worker is available to discuss social needs with patients via a "warm handoff," in which the primary care pediatrician introduces the social worker or community health worker to the patient during the visit or phone call. With the eventual use of a web-based platform that facilitates communication between the clinic and local community organizations, electronic referrals will ultimately be made to area resources.

INTERVENTIONS

For screening to be worthwhile, it is essential to identify resources and to provide support for patients whose screens are positive. Such interventions may be generalized, addressing multiple social determinants of health, or targeted, addressing particular domains. Several evidence-based programs have been developed to help patients.

General Interventions Addressing Multiple Social Determinants of Health

Practices may provide a handout for patients containing information about local services, community organizations, and programs that address multiple social determinants of health. In the WE CARE model, a family resource guide specific to the community of the health center contains perforated patient handouts listing community resources for various needs. Providers give the handouts to their patients, and clinic staff help patients apply for services. Studies of the WE CARE model have shown that patients who are screened for social determinants and referred to resources based on their needs are more likely to be enrolled in community resources than are patients who are not screened and referred. (10)

Creating and updating a resource guide, however, is challenging for busy pediatric practices. To facilitate this effort, practices may work together with public health agencies, community programs, and other members of their AAP chapters. Furthermore, several online tools and telephone hotlines have been established to help connect providers to community resources, which are summarized in Table 2. Note that several of these resources are commercial products that we mention as options for pediatricians but that we do not specifically endorse.

Patients may also be referred to programs embedded in the clinic. A clinic may have an in-house social worker to help patients connect to services as well as to provide counseling for patients and families struggling with mental illness. Through the Medical-Legal Partnership, physicians and attorneys partner to help patients with social and legal issues. In this model, a lawyer may meet with patients directly in the clinic, may be available as a consultant for physicians, or may take a patient as a pro bono client. Studies have shown that medical-legal partnerships have a positive effect on patient well-being, use of health-care services, patient empowerment, and legal problem-solving abilities. (8)(11) Health Leads is a national program, funded by corporate and private donors, in which patients who screen positive are referred by their providers to advocates in the clinic who help them connect to community resources as well as to government benefits programs. Studies have shown that Health Leads has been successful in ensuring that families' social needs are met. (8)(12) In addition, community health workers, who are trusted members of the community, can serve as integral members of a clinic team because they are able to overcome cultural and economic barriers to address social determinants of health that limit patients' access to health care. The integration

TABLE 2. **Resources**

RESOURCE	DESCRIPTION	WEBSITE
Help Me Grow	• Links providers with community organizations • Maintains a phone line and resource center for providers and patients • Available in 23 states	https://helpmegrownational.org
The Children's Advocacy Project (CAP4Kids)	• Enables providers to create online patient handouts of local organizations and services in 13 communities • Providers can update the directories provided by the website	http://cap4kids.org/whatiscap4kids.html
HelpSteps	• Online screening tool, specific to Boston, Massachusetts, that patients can use while in the waiting room to search for local social services	https://www.helpsteps.com/home.html
Healthify	• Tablet-based tool developed for self-administration by patients while in the waiting room that transmits a list of social needs to the clinician electronically • Provides patients with a list of local community and governmental resources, and sends follow-up text messages • This tool is a commercial product that we mention as an option but that we do not specifically endorse	https://www.healthify.us/platform
Aunt Bertha	• Comprehensive online platform that assists providers and patients to find local community programs and services across the United States through a zip code search function	www.auntbertha.com
Community Services Locator	• Connects providers and families to various social services, including child care, early childhood education, special education services, income support, wellness programs, and parenting programs • Maintained by the National Center for Education in Maternal and Child Health	https://www.ncemch.org/knowledge/community.php
United Way	• Phone line and website for families to find resources for housing, employment, food, and health care (including addiction, trauma, and other mental health services)	http://www.211.org/
Reach Out and Read	• Program that promotes early language development and literacy	http://www.reachoutandread.org/
Healthy Steps for Young Children	• Program that focuses on child development and parenting skills • Must be a member of Healthy Steps to view resources on the website	http://healthysteps.org/
The Incredible Years	• Program that focuses on child development and parenting skills • This tool is a commercial product that we mention as an option but that we do not specifically endorse	http://incredibleyears.com/
Triple P	• Program that focuses on child development and parenting and teaching skills • This tool is a commercial product that we mention as an option but that we do not specifically endorse	http://www.triplep-parenting.com/us-en/triple-p/
The Medical-Legal Partnership	• Partnership of physicians and attorneys to help patients with social and legal issues	http://medical-legalpartnership.org/

of community health workers into health-care settings has been shown to directly lead to cost-savings, decreased emergency department visits, and improvement in quality of life. (13) Clinic-based practices may also use trained volunteers, such as AmeriCorps volunteers or undergraduate students, to serve as liaisons between busy clinicians and families to facilitate referrals to community resources. (14) The availability of such in-person navigators has been shown to help families meet social needs and to improve children's overall reported health status. (15)

Targeted Interventions Addressing Specific Social Determinants of Health

Food Insecurity. Food pantries co-located in hospitals have been developed to address the issue of food insecurity. Providers from clinics affiliated with the hospitals can refer their patients to the pantries. Boston Medical Center was one of the first hospitals to open a food pantry. Patients who are referred to the pantry receive customized bags of food, based on their medical conditions, and are able to visit the food pantry twice a month. The pantry has expanded to include a demonstration kitchen where patients can learn how to cook nutritious foods in healthy ways. (16) Similarly, clinicians and local food banks have collaborated in the establishment of community-based food pharmacies, which take prescriptions from clinicians for specific nutritional items for children with medical conditions, which are exacerbated by nutritional deficiencies. (17) Health centers have also experimented with bringing community supported agriculture programs to their clinics to provide fresh produce to their patients, combatting food insecurity, poor nutrition, and obesity. (17) Furthermore, waiting room materials describing the Supplemental Nutrition Assistance Program (SNAP) incentive programs, through which SNAP funds can be used at higher value at farmers markets, have been successful at addressing financial barriers to food security and have significantly increased fruit and vegetable consumption. This behavior change has been sustained even after the financial incentive is no longer available. (18)

Income. Tax preparation programs at pediatric clinics, staffed by volunteers, help families access tax credits that they did not previously receive, particularly the Earned Income Tax Credit (EITC). Many families are eligible but do not receive this benefit due to lack of knowledge, tax complexities, or inadequate assistance. The EITC helped lift 1.7 million children out of poverty in 2013 and is associated with a significant reduction in infant mortality. (19)(20)

Child Care. Child care vouchers, funded through a combination of federal and state programs, administered by states, and delivered by local agencies, allow low-income families to work or attend school. However, use of child care subsidies among eligible families is low (7%–34%) due to lack of knowledge about available subsidies, burdensome paperwork, and stigma. (21) Availability of child care subsidy applications or screens for eligibility in the waiting room may assist low-income families in navigating these barriers.

Housing. Several projects have been developed to address issues of housing and homelessness. A pilot study in Boston is evaluating the impact of "housing prescriptions" (referrals to a case management organization in the community that assists with housing) on housing stability, emergency department utilization, health-care compliance, mental health, and food security. (22) An intervention using community health workers to perform in-home environmental assessments, providing other social supports, and advocating for improved housing conditions resulted in decreased asthma-related urgent care use and fewer days with asthma symptoms, with significant projected cost-savings. (23) Community health workers can also help homeless clients and families complete and file paperwork for the local housing authority and can follow up and track patients experiencing homelessness. (13)

Lead exposure has become an increasingly concerning housing issue for families with young children, as we have learned that there is no safe lead level and given the recent contamination of drinking water in Flint, Michigan. The AAP's lead exposure and lead poisoning initiative provides pediatricians with information about the effects of lead poisoning on children, resources they may distribute to families, and opportunities for advocacy. (24) In addition, the Centers for Disease Control and Prevention's (CDC's) Lead Poisoning Prevention Program is an integral resource for families and health-care providers. This program provides information about childhood lead poisoning, allows the public to access national and local surveillance data, provides links online to tools and training about lead, and maintains a list of lead poisoning prevention programs by state. (25)

Literacy. Reach Out and Read is a program that promotes early language development and literacy. The program includes providing waiting room activities, counseling caregivers on the benefits of reading to their children, and giving age-appropriate books to children at each health supervision visit from 6 months through 5 years old. Reach Out and Read has been shown to increase the frequency with which parents and children read together, increase the number of children's books present in families' homes, and improve children's expressive and receptive language scores. (8)(26)

The Video Interaction Project is another program that aims to enhance early language development and literacy as well as cognitive and social-emotional development. In this program, during health supervision visits, a mother and child are recorded on video, a child life or child development specialist reviews the video with the mother, and together they identify positive interactions and areas for improvement. The mother takes the video home after each health supervision visit. Studies have demonstrated that this program improves children's cognitive development and reduces symptoms of maternal depression. (8)(27)

Public libraries provide free membership and programs for children to community residents, and pediatric clinics can be instrumental in connecting patients and families to the local library. Public library use has been found to be associated with higher rates of reading aloud between parents and children. (28)

Parenting Skills. Healthy Steps for Young Children is a program that focuses on child development and parenting skills. Healthy Steps specialists meet with families during health supervision visits as well as separately to discuss issues of development, behavior, and safety. The program may also include home visits and parent support groups. Healthy Steps has been shown to improve quality of care and to enhance parenting skills. (8)(29)

Our Practice

We have several interventions embedded in our clinics for patients who screen positive for poverty-related social determinants of health. Social workers meet with patients who report food insecurity, housing instability, and other financial difficulties. Our clinics have an on-site attorney to whom patients struggling with immigration status, difficulties with landlords, and other legal issues can be referred. Through state-sponsored funding, our clinics have hired community health workers, who can refer our patients to food pantries, housing organizations, employment centers, immigration aid, and other social service programs. To help alleviate food insecurity, health educators at our clinics distribute Health Bucks to patients, a city-sponsored food voucher that can be used to purchase fresh produce at farmers markets. A co-located Medicaid office facilitates referrals for parents and children who are struggling with insurance coverage issues. Through Reach Out and Read, patients 6 months to 5 years old receive a new book at every health supervision visit.

ADVOCACY

In addition to providing resources and establishing effective interventions, pediatricians may advocate for government policies and programs aimed at reducing the toxic effects of poverty. The AAP and APA reference several important programs that pediatricians can urge local and national representatives to support. The EITC and Temporary Assistance for Needy Families are programs that increase the earnings of low-income families. Children with special health-care needs may be eligible for Supplemental Security Income, of which parents may not be aware. The SNAP, the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), the National School Lunch Program, and the Summer Food Service Program (when school is not in session) help families struggling with food insecurity. Early Head Start, Head Start, and the Early Childhood Home Visiting Program promote early childhood education, child development, and literacy. (3)(8)

Although these programs are well established, many families who are eligible are not enrolled because they do not know they qualify and because they do not know how to apply. Therefore, in addition to contacting government representatives to advocate for these programs, pediatricians may provide families with online links to the programs and perhaps further information about eligibility and the application process. (8) Furthermore, pediatricians are instrumental in educating families with undocumented parents that children born in the United States are eligible for most government benefits, including WIC and SNAP, and that undocumented children are eligible for several benefits as well, such as free school lunch and government-sponsored insurance, depending on the state. (30) Table 3 lists federal websites that can serve as resources.

Pediatricians may also advocate for raising of the minimum wage in their local city and state governments, for paid family leave and paid sick leave, and for continued funding of child care subsidy programs, all of which will prevent working families from crossing into poverty.

The AAP maintains a federal advocacy website where pediatricians can find information about key advocacy issues and health-care coverage fact sheets by state (https://www.aap.org/en-us/advocacy-and-policy/federal-advocacy/Pages/Federal-Advocacy.aspx). For pediatricians with a greater interest in advocacy, the AAP has a listserv that sends timely federal updates via e-mail. To sign up, providers can e-mail *kids1st@aap.org*.

Our Practice

Many of our pediatricians are actively involved in advocacy. A group of pediatricians from our institution travels to Albany to attend the AAP Advocacy Day each year to meet with state representatives about policies we feel are crucial to the health of our patients. Our pediatric residents have

TABLE 3. **Federal Programs**

FEDERAL PROGRAM	DESCRIPTION	ELIGIBILITY CRITERIA (2017)[a,b]	WEBSITE
Medicaid/Children's Health Insurance Program (CHIP)	• Medicaid provides health coverage for low-income individuals and families • CHIP provides low-cost health coverage to children in families that earn too much money to qualify for Medicaid • Each state has the option to cover its CHIP population within its Medicaid program, design a separate CHIP program, or establish a combination program • Jointly funded by state and federal governments and managed by states	• Annual gross income <200% the federal poverty level (FPL) in 3 states, 200%–300% FPL in 29 states, and ≥300% FPL in 19 states, including DC • US citizen or qualified immigrant[c] • Some states may use state funding to help cover low-income non-qualified immigrant children • Low-income non-qualified immigrant children eligible for *emergency Medicaid* in all states	https://www.medicaid.gov/medicaid/eligibility/index.html https://www.medicaid.gov/chip/eligibility-standards/index.html https://www.kff.org/medicaid/fact-sheet/where-are-states-today-medicaid-and-chip/
Earned Income Tax Credit (EITC)	• Federal antipoverty tax credit for working people with low to moderate income, particularly those with children	• Annual gross income ∼<220% FPL • US citizen or qualified immigrant	https://www.irs.gov/credits-deductions/individuals/earned-income-tax-credit
Temporary Assistance for Needy Families (TANF)	• Provides cash assistance to needy families with children. • Administered by state government through federal block grant	• Dependent child • Gross monthly income below ∼16%–107% FPL, depending on state • US citizen or qualified immigrant[c]	https://www.acf.hhs.gov/ofa/programs/tanf
Supplemental Security Income (SSI)	• Provides benefits to disabled adults and children who have limited income and resources	• Child fits strict definition of disability (physical/mental condition that very seriously limits activities AND condition expected to last 1 y or result in death) • Child and family income/resource limits, varies by state • US citizen or qualified immigrant[c]	https://www.ssa.gov/disabilityssi/ssi.html
Supplemental Nutrition Assistance Program (SNAP)	• Federal nutrition assistance to low-income families; formerly known as the Food Stamp Program	• Gross monthly income <130% FPL • Limited financial reserves (<$2,250) in some states • US citizen or qualified immigrant[c]	https://www.fns.usda.gov/snap/eligibility
Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)	• Federal grant to states for supplemental foods for low-income pregnant and postpartum women, infants, and children	• Women must be pregnant, breastfeeding, or nonbreastfeeding postpartum (up to 6 mo) • Infants and children aged <5 y • Gross monthly income <185% FPL • No citizenship or legal residency requirements	https://www.fns.usda.gov/wic/wic-eligibility-requirements
National School Lunch Program (NSLP)/Summer Food Service Program	• Federally assisted meal program operating in schools to provide nutritionally balanced low-cost or free lunches to children	• Child enrolled in a public or participating private school • Reduced priced meals: gross monthly income <185% FPL • Free meals: gross monthly income <130% FPL • No citizenship or legal residency requirements	https://www.fns.usda.gov/nslp/national-school-lunch-program-nslp

Continued

TABLE 3. (Continued)

FEDERAL PROGRAM	DESCRIPTION	ELIGIBILITY CRITERIA (2017)[a,b]	WEBSITE
Head Start/Early Head Start	• Promotes school readiness of young children from low-income families through agencies in the local community	• Infants and children aged <5 y • Gross annual income <100% FPL; some exceptions for income 100%–130% FPL, depending on state and availability • Homeless children, children in foster care, and children from families that receive TANF eligible regardless of income • No citizenship or legal residency requirements	https://www.acf.hhs.gov/ohs

[a] *The 100% FPL for a family of 4 is defined as an annual income of $24,600 in 2017 in the 48 contiguous states, excluding Alaska and Hawaii (federal poverty guidelines differ in these states).*

[b] *Qualified immigrant includes lawful permanent residents (LPR/Green Card Holder); asylees/refugees; Cuban/Haitian entrants; people paroled into the United States for at least 1 year; conditional entrant granted before 1980; battered noncitizens, spouses, children, or parents; victims of trafficking and their spouse, child, sibling, or parent or individuals with a pending application for a victim of trafficking visa; granted withholding of deportation; and member of a federally recognized Indian tribe or American Indian born in Canada.*

[c] *May have a 5-year waiting period, varies by state.*

attended 1-day and 3-day legislative conferences in Washington, DC, to learn effective lobbying skills and to meet with members of Congress to advocate for national-level issues. Faculty and residents have also participated in an annual city-based advocacy conference, hosted by a local academic institution, to facilitate an exchange of ideas regarding advocacy and to hear from various community organizations.

CONCLUSION

The patient described in the case scenario herein was referred to the clinic's onsite attorney. The attorney obtained a letter from the patient's primary pediatrician explaining the necessity for heat and hot water in controlling the patient's asthma. Once the letter was completed, the attorney contacted the building manager of the shelter to request that the heat and hot water in the apartment be repaired. Three weeks later, the repairs were made. The patient went to the emergency department 1 additional time for an asthma exacerbation before the completion of the repairs and has not been back to the emergency department since then.

Although there is abundant evidence about the implications of poverty-related social determinants on children's health, more research is needed to understand the optimal ways to screen for social determinants of health, the most effective interventions to address them, and the most powerful ways to advocate for government policies and programs aimed at reducing the harmful effects of poverty. The known negative effects of poverty, homelessness, food insecurity, and other social factors on health, however, compel us, as pediatric providers, to screen, provide interventions, and advocate despite lack of rigorous evidence. In the words of Bernard Dreyer, MD, past-president of both the AAP and the APA, "poverty is the most significant non-communicable disease children are suffering from today." Pediatric providers' shared passion to mitigate the effects of childhood poverty on the lifelong trajectory of health, bolstered by partnerships with community agencies as well as by state and federal advocacy efforts, together have the potential to transform the lives of millions of children.

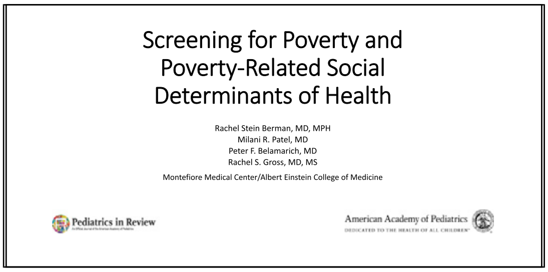
ACKNOWLEDGMENTS

The authors would like to thank Drs Yonit Lax and Sandra Braganza for their work on the IHELLP initiative through the Social Pediatrics Residency Program; and Julie Brandfield, Esq, associate director of LegalHealth of the New York Legal Assistance Group, for her assistance with the case scenario and recommendations for screening tools.

Summary

- On the basis of strong research evidence, poverty-related social determinants of health have a deleterious effect on children's health. (3)(7)(8)
- On the basis of some research evidence as well as consensus, pediatricians are encouraged to screen for poverty and poverty-related social determinants of health. (10)
- On the basis of strong research evidence, several effective interventions have been established that pediatricians may adopt in their practices to address poverty and poverty-related social determinants of health. (8)(10)(12)(16)
- On the basis of consensus due to lack of relevant clinical studies, pediatricians are encouraged to advocate for government policies and programs aimed at eliminating poverty and poverty-related social determinants of health on children and families.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/5/235.supplemental.



Screening for Poverty and
Poverty-Related Social
Determinants of Health

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Pediatrics in Review

American Academy of Pediatrics
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References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/39/5/235.

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1. You are the director of an inner city clinic that has recently opened. You are in the process of organizing a clinic protocol that adheres to addressing social determinants of health as put forth by the American Academy of Pediatrics. Which of the following is not considered a social determinant of health?
   - A. Food security.
   - B. Income.
   - C. Legal immigration status.
   - D. Length of time in current housing.
   - E. Religious belief.
2. You would like to administer a screening questionnaire for social determinants of health in your clinic. Presently your city-based clinic does not have the staffing, and neither do you have the time in your clinic schedule to directly administer a questionnaire or additional questions to your patients during the 15-minute time allotted for a new patient office visit. Which of the following questionnaires would be the most appropriate to implement in this situation?
   - A. Accountable Health Communities Core Health-Related Social Needs Screening Tool.
   - B. Reach Out and Read.
   - C. The Medical-Legal Partnership.
   - D. IHELLP (Income, Housing, Education, Legal Status, Literacy, Personal Safety).
   - E. SWYC (Survey of Well-Being of Young Children) Family Questions.
3. You are a pediatrician in a community clinic. You are seeing a new patient for a routine health supervision visit. The Health Leads screening tool is administered and the patient screens positive. Otherwise, the patient has no acute medical or physical problems. Referral of this patient to be seen by which of the following professionals is the most appropriate next step in management?
   - A. Child life therapist.
   - B. Community worker.
   - C. Nutritionist.
   - D. Physical therapist.
   - E. Psychologist.
4. You are caring for a 3-year-old boy with Down syndrome in your pediatric clinic. The family income is below the federal poverty level. Compared with a family with the same income level but with a developmentally normal child who does not have Down syndrome, which of the following additional programs would the family of this child uniquely qualify for?
   - A. Early Head Start.
   - B. Earned Income Tax Credit (EITC).
   - C. Supplemental Security Income.
   - D. Temporary Assistance for Needy Families (TNAF).
   - E. Women, Infants, and Children (WIC).
5. You are caring for a 1-year-old boy in your clinical practice who is "undocumented," as are both parents. Which of the following programs would this child most likely be eligible for?
   - A. EITC.
   - B. Free school lunch.
   - C. Supplemental Nutrition Assistance Program (SNAP).
   - D. TNAF.
   - E. WIC.

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Bordetella pertussis (Pertussis)

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Education Gaps

1. Clinicians must understand the changing epidemiology of pertussis and the reasons for the endemic and epidemic nature of infection despite widespread vaccination.
2. Clinicians must understand the strategies developed to prevent pertussis in those who are at high risk for complications.

Objectives After completing this article, readers should be able to:

1. Recognize the antigenic components of pertussis.
2. Understand the changing epidemiology of the disease and the major factors contributing to this change.
3. Describe the clinical features during the natural progression of pertussis and the complications of infection.
4. List the options for laboratory testing of pertussis and their respective limitations.
5. List the recommended agents for antimicrobial treatment and postexposure chemoprophylaxis of pertussis.
6. Understand the rationale for the current pertussis vaccine recommendations.

AUTHOR DISCLOSURE Drs Daniels and Sabella have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
DTaP	diphtheria, tetanus, and acellular pertussis vaccine
DTwP	diphtheria, tetanus, and whole cell pertussis vaccine
IHPS	infantile hypertrophic pyloric stenosis
PCR	polymerase chain reaction
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
Th	T-helper

INTRODUCTION

Bordetella pertussis is a fastidious gram-negative coccobacillus responsible for the respiratory infection commonly known as "whooping cough." The organism is spread by respiratory droplets and is highly contagious among close contacts. The typical incubation period is 7 to 10 days, but it may be as long as 21 days. Neither natural infection nor pertussis vaccination results in long-lasting immunity, contributing to endemic infection and 3- to 5-year cycles of pertussis epidemics.

PATHOGENESIS

Several active components, which play a role in immunity and are responsible for the organism's ability to cause disease, are produced by *B pertussis*. (1) Pertussis toxin, filamentous hemagglutinin, pertactin, and agglutinogen allow the organism to adhere to ciliated epithelium of the respiratory tract, where it exerts its effects.

Pertussis toxin also induces cell cytoxicity, inhibits neutrophilic and monocytic responses, and delays induction of specific immune responses. Pertussis toxin is postulated to be responsible for the systemic manifestations of pertussis, including the leukocytosis and lymphocytosis evident in young infants. This virulence factor is also thought to sensitize β-islet cells in the pancreas, which may lead to hyperinsulinism, which rarely manifests as hypoglycemia in young infants. Other substances elaborated by the organism include adenylate cyclase and tracheal cytotoxin, which allow the bacteria to cause damage to the respiratory epithelium and evade the host immune system by altering leukocyte function. Pertussis vaccines contain these various antigenic components. Central nervous system complications of pertussis are thought to be secondary to hypoxemia induced by coughing and apnea associated with infection rather than to a direct effect on the central nervous system by the organism. (2)

EPIDEMIOLOGY

In the 1940s, before the introduction of pertussis vaccine in the United States, there were 100,000 to 200,000 cases of whooping cough and thousands of deaths annually. After the introduction of pertussis vaccine, there was a 99% decrease in the number of cases; the lowest number of cases was in 1976, with only 1,010 cases reported. Over the past few decades there has been an increasing incidence of pertussis (Fig 1). According to the Centers for Disease Control and Prevention (CDC), there were 48,277 cases reported in the United States in 2012, the highest number of cases since 1955. (3) Worldwide, pertussis is responsible for 16 million cases and approximately 195,000 deaths annually. (4)

Historically, the incidence of pertussis peaked in children 1 to 5 years of age and was less common in those younger than 1 year and older than 10 years. There has been a shift in recent decades with an increase in the incidence among infants younger than 1 year, adolescents, and adults (Fig 2). In 2015, 55% of reported pertussis cases in the United States were in individuals older than 10 years, and children younger than 1 year accounted for 13% of cases. (5)

There are multiple factors that seem to be responsible for the change in epidemiology of pertussis: the switch from whole cell pertussis vaccine to acellular pertussis vaccine, waning immunity, change in the organism, vaccine refusal, lack of natural disease to boost immune response, and undiagnosed individuals serving as reservoirs.

Switch from Whole Cell Pertussis Vaccine to Acellular Pertussis Vaccine

Concerns about the reactogenicity of the diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTwP) lead to the development and introduction of the diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). The DTaP was incrementally introduced into the US pediatric immunization schedule starting in 1992, with all children receiving only the DTaP by 1997. (6) Acellular pertussis vaccines are significantly less reactogenic than whole cell vaccines.

Recent studies during epidemic outbreaks in Australia demonstrated that children who received the DTwP series

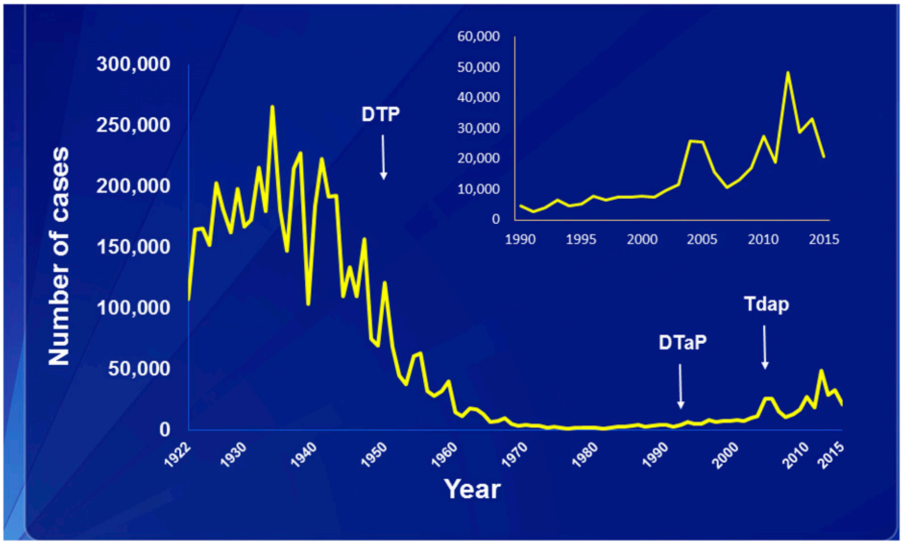


Figure 1. Reported pertussis cases, 1922-2015. From the Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System for 1950 through 2015 and from passive reports to the Public Health Service from 1922 through 1949.
DTP=diphtheria, tetanus toxoids, and pertussis vaccine, DTaP=diphtheria, tetanus, and acellular pertussis vaccine, Tdap=tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

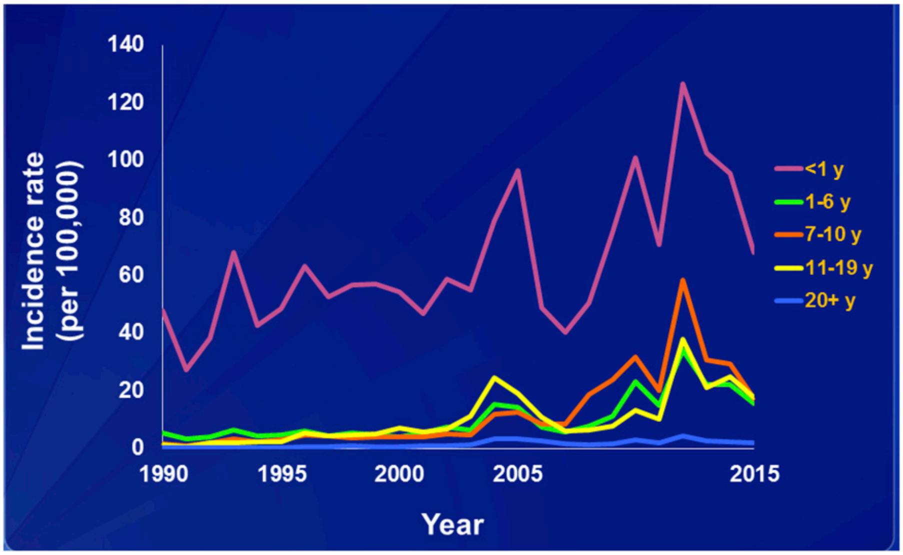


Figure 2. Pertussis incidence by age group, 1990-2015. From the Centers for Diseases Control and Prevention National Notifiable Diseases Surveillance System.

had lower rates of pertussis than those who received the DTaP series. (7) This effect may be related to the different responses elicited by the 2 types of vaccines: the whole cell pertussis vaccine activates T-helper (Th) type 1 cells, and the acellular pertussis vaccine elicits a Th2 response. The Th1 responses result in robust interferon-γ production, which is required for cell-mediated immunity and rapid clearance of the organism on repeated exposure, whereas Th2 responses do not seem to have the same effect on interferon-γ, resulting in less effective clearing of the organism from the respiratory tract after infection. Thus, humoral immunity provided by acellular pertussis vaccines seems to be effective at preventing severe disease but may lack the cellular responses needed to effectively eradicate the infection from the respiratory tract. (7)(8)(9)(10)(11)(12)(13)(14)

Waning Immunity

Neither natural infection nor vaccination induces lifelong immunity. Recent studies demonstrate that immunity wanes 4 to 20 years after natural infection and 4 to 12 years after vaccination. (15) After pertussis outbreaks in California in 2010 and 2014, it was determined that patients who developed pertussis were more likely to have had a longer period of time since their last DTaP or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap). (16)(17) More specifically, immunity began to wane 5 years after the last DTaP, with a 42% increase in the odds of developing pertussis each year thereafter. (16) These studies also determined that immunity began to wane 2 to 3 years after Tdap vaccination. (17) Another study showed that the odds of pertussis increased 1.33 times per year after the last DTaP, with only an estimated 10% of children retaining immunity 8.5 years after the last immunization. (18)

Change in the Organism

Current vaccines contain various antigens to components of *B pertussis,* such as pertussis toxin, fimbriae, pertactin, and filamentous hemagglutinin. Since the introduction of the whole cell and acellular vaccines there have been genetic changes of *B pertussis*. Variants that are emerging include allele changes to the genes that code for pertactin (*prn2*), pertussis toxin promoter (*ptxP3*), and fimbriae (*Fim3*). (6)(19)(20)(21) Studies in Europe and Asia have demonstrated that current pertussis strains are different from when the vaccines were developed, which may be limiting the memory provided by vaccination. (20)(21) In addition, the adaptation of these components may make the organism more virulent and adept to evade the immune response. (19)

Vaccine Refusal

There is concern that vaccine hesitancy or refusal has contributed to the resurgence of preventable diseases, especially measles and pertussis. Phadke et al (22) reviewed the analysis of 32 pertussis outbreaks and found high percentages of unvaccinated individuals (24%–45%) in the states with the largest outbreaks, with a significant proportion of individuals (59%–93%) unvaccinated by choice.

Lack of Natural Disease to Boost Immune Response

Some have proposed that with decreased rates of pertussis since vaccine development there are fewer cases of pertussis to which an individual is exposed during their life, thereby limiting the chance to naturally boost the immune memory to the infection. Without these exposures to less severe cases, an individual's immunity continues to wane without a boosted response. (15)

Undiagnosed Individuals Serving as Reservoirs

Last, adolescents and adults with pertussis may not manifest classic or severe symptoms of pertussis, resulting in underreporting of infection in these age groups. These individuals, however, serve as important reservoirs of infection and commonly transmit pertussis to infants and younger children who are unvaccinated or have been incompletely vaccinated or who may have waning immunity after vaccination. (23) Several studies have documented that adolescents and adults have an important role in transmission of the organism and that pertussis is a common cause of prolonged cough illness in these individuals. (24)(25)

CLINICAL PRESENTATION

Pertussis is typically divided into 3 stages: catarrhal, paroxysmal, and convalescent. Progression through these stages and symptoms varies among individuals, especially based on the patient's age.

Catarrhal Stage

The catarrhal stage typically begins 1 to 2 weeks after exposure to *B pertussis*. Symptoms at this time are nonspecific (cough, coryza, and low-grade fever) and may be confused with an upper respiratory tract infection. During this 1- to 2-week phase, individuals are contagious without realizing that they have pertussis. Infants may have a very short catarrhal phase before progressing to the next stage.

Paroxysmal Stage

Classical symptoms of whooping cough begin to be evident during this stage, which can last approximately 1 month. Children develop paroxysmal episodes of cough followed by an inspiratory "whoop" sound at the end of the episode. This high-pitched whoop sound is caused by rapid airflow during a forced inhalation after a repetitive coughing episode during which the lung is devoid of air and the glottis is partially closed. During the coughing episodes, cyanosis, especially perioral cyanosis in young children, and posttussive emesis are common; however, between episodes infants and children generally appear well. Individuals with pertussis may experience fatigue and exhaustion from lack of sleep and decreased appetite caused by persistent coughing. Fever is characteristically absent during pertussis infection; its presence should prompt a search for secondary bacterial infection.

Infants and older individuals may have less classic symptoms during this stage. Infants may present with apnea, cyanosis, and gagging during the coughing spell without the classical whoop sound. Adolescents and adults also may lack the typical whoop sound at the end of coughing spells; however, the presence of a whoop sound or posttussive emesis in adults should raise suspicion for pertussis. (26)

Convalescent Stage

Diminished severity and frequency of cough paroxysms characterize this stage, which signify recovery from pertussis. However, because pertussis is also known as "the 100-day cough," this stage can last from weeks to months and is often exacerbated by intercurrent respiratory illness, especially in infants.

DIFFERENTIAL DIAGNOSIS

Adenovirus

Adenovirus can cause an illness of severe prolonged paroxysmal cough associated with an inspiratory whoop and posttussive emesis. The presence of pharyngitis, conjunctivitis, gastrointestinal symptoms and fever commonly associated with adenovirus infection can help distinguish this from pertussis.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of prolonged cough and pneumonia in school-aged children. The presence of other systemic symptoms, such as fever and pharyngitis, along with auscultatory (crackles) and chest radiographic findings can help differentiate this from pertussis.

Chlamydia trachomatis

Infants with *Chlamydia trachomatis* pneumonia may have a cough illness that may be difficult to distinguish from pertussis. The cough is more commonly described as a staccato cough, with inspiration between each cough. These infants may also have tachypnea and crackles, and 50% of them have a history of conjunctivitis. On laboratory evaluation they commonly have a normal white blood cell count and an elevated eosinophil count.

Respiratory Syncytial Virus

Respiratory syncytial virus is a common cause of respiratory infection in infants and may present with cough and apnea. Wheezing, fever, and significant rhinorrhea or congestion may help differentiate this from pertussis. Coinfection with pertussis and respiratory syncytial virus is well described.

Other *Bordetella* Species

Bordetella parapertussis causes a pertussis-like syndrome and accounts for approximately 5% of *Bordetella* isolates in the United States. Compared with *B pertussis*, the paroxysms and whoop are less severe, the posttussive emesis is less frequent, and the total duration of cough is shorter. (27)

COMPLICATIONS AND OUTCOMES

Young infants (<6 months old) with pertussis have the highest rates of morbidity and mortality compared with older infants, children, and adolescents. Complications in these young infants include secondary bacterial pneumonia, apnea, bradycardia, and pulmonary hypertension. Bacterial pneumonia is the most common complication of pertussis, occurring in approximately 5% of all cases and in approximately 10% to 25% of infants younger than 6 months. During coughing spells, infants may become hypoxic, leading to central nervous system complications, including seizures and encephalopathy. (2) Because of its propensity to cause apnea in young infants, pertussis has been proposed as a cause of sudden infant death syndrome. (28)

Additional complications include otitis media, dehydration, conjunctival/scleral hemorrhages, petechiae, rib fractures, subcutaneous emphysema, and pneumothorax.

DIAGNOSIS (TABLE 1)

Culture

Until recently, the gold standard for diagnosing pertussis was a positive respiratory culture for *B pertussis*. Culture also allows for strain typing and antimicrobial testing, which is useful for public health tracking. Culturing for the organism, however, is fraught with difficulty because it requires obtaining a sample within the first 2 weeks of illness, using a specific swab (calcium alginate or Dacron-tipped swab) for collection, immediate inoculation on solid media or transport in special media (Stainer-Scholte broth with cyclodextrin or Regan-Lowe semisolid transport media), and incubation at 95°F to 98.6°F (35°C–37°C) for 7 days, to maximize the yield for isolating the organism. Previous immunization or recent antimicrobial treatment can lower the yield of the culture.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) testing is the “new” gold standard and is now more commonly used to diagnose pertussis because it allows for a more rapid result and seems to be more sensitive than culture, especially in individuals who are mildly symptomatic and in those who received antibiotics. It requires collection of a nasopharyngeal specimen using a Dacron swab or nasopharyngeal aspirate. The PCR test is most sensitive if obtained within the first 3 to 4 weeks of illness. (29) Overall sensitivity and specificity vary based on the performing laboratory, and it is important to note that there is no standard PCR assay. False-positives may occur due to contamination from other samples.

Serology

Serologic testing is helpful in epidemiologic studies of pertussis but have a limited role in the clinical setting.

TABLE 1. **Diagnostic Testing for Pertussis**

TEST	TIMING	ADVANTAGES	DISADVANTAGES	COMMENTS
Culture	First 2 wk of illness	100% specific; allows for strain typing for public health tracking	Difficult to grow, especially with history of treatment or vaccination; results delayed (∼1 wk)	Must be collected on Dacron or calcium alginate swab with immediate plating on appropriate media or transport media
Polymerase chain reaction (PCR)	Within the first 3–4 wk of illness	More rapid results, does not require live bacteria	False-positives and false-negatives; no standard PCR assay; laboratory dependent	Cannot use calcium alginate swab to collect
Serology	After 2 wk of symptoms	May be helpful later in the course of the illness if rising titer or seroconversion	Not sensitive or specific; no defined cutoff values for positive tests	Not used for diagnostic purposes; used for epidemiologic studies
Direct fluorescent antibody			No longer recommended	

Adapted with permission from Centers for Disease Control and Prevention Pertussis Laboratory Testing.

Acute and convalescent titers against pertussis antigens are generally required for serologic diagnosis. However, such testing is difficult to interpret in immunized individuals, specific cutoff data are not available, and these tests are not licensed for commercial use.

Direct Fluorescent Antibody Testing

Direct fluorescent antibody testing of nasopharyngeal specimens for pertussis antigens is no longer recommended. These tests have poor sensitivity compared with culture and PCR and require experienced laboratory personnel.

Supporting Laboratory Testing and Imaging

Leukocytosis, specifically absolute lymphocytosis, is common in infants and young children with pertussis, especially in the late catarrhal and paroxysmal stages. The degree of lymphocytosis correlates with the severity of disease. (30)(31)(32) The presence of absolute lymphocytosis in the setting of an appropriate clinical scenario should raise suspicion for the possibility of pertussis, keeping in mind that normal lymphocyte counts vary with age. Thrombocytosis is common and correlates with a poorer prognosis in infants. Chest radiography may reveal nonspecific findings, such as hyperinflation and perihilar infiltrates, but most often is normal.

MANAGEMENT

Antimicrobials

Antimicrobial therapy (Table 2) is recommended to eliminate the organism from the nasopharynx and, thus, reduce transmission of the organism. In general, antimicrobial therapy does not influence the clinical course of pertussis, although it may reduce the duration and severity of symptoms if administered before the paroxysmal stage. A recent case-control study of infant deaths from pertussis concluded that early recognition and appropriate antibiotic therapy are important in preventing death. (33) Therapy should be given to any infant younger than 1 year within the first 6 weeks of symptoms and anyone older than 1 year within the first 3 weeks if pertussis is suspected. (34)

Macrolides (azithromycin, clarithromycin, and erythromycin) are the preferred class of antibiotics to treat pertussis. Azithromycin is most commonly used because it has less adverse effects and is easier to administer. When

TABLE 2. **Therapeutic and Chemoprophylactic Options for Pertussis**

AGENT	INFANTS (<1 MO)	INFANTS (1–5 MO)	CHILDREN (>6 MO)	ADULTS	NOTES
Primary Therapy					
Azithromycin (first line, drug of choice)	10 mg/kg once daily × 5 d	10 mg/kg once daily × 5 d	Day 1: 10 mg/kg (max, 500 mg) once; days 2–5: 5 mg/kg (max, 250 mg) once daily	Day 1: 500 mg Days 2–5: 250 mg	Preferred agent. Caution in patients with underlying cardiac disease (can prolong QTc)
Erythromycin	Not recommended	40–50 mg/kg per day (max, 2 g/d) divided 4 times daily × 14 d	40–50 mg/kg per day (max, 2 g/d) divided 4 times daily × 14 d	2 g/d divided 4 times daily × 14 d	Gastrointestinal adverse effects
Clarithromycin	Not recommended	15 mg/kg per day (max, 1 g/d) divided twice a day × 7 d	15 mg/kg per day (max, 1 g/d) divided twice a day × 7 d	1 g/d divided twice a day × 7 d	Not palatable
Alternative Agent					
TMP-SMX	Contraindicated in infants <2 mo of age	TMP 8 mg/kg per day (max, 320 mg/d); SMX 40 mg/kg per day divided twice a day × 14 d **Contraindicated in infants <2 mo of age*	TMP 8 mg/kg per day (max, 320 mg/d); SMX 40 mg/kg per day divided twice a day × 14 d	TMP 320 mg; SMX 1,600 mg/d divided twice a day × 14 d	Contraindicated in infants <2 mo old

Max=maximum, TMP-SMX=trimethoprim-sulfamethoxazole.

Adapted with permission from Tiwari T, Murphy TV, Moran J, et al; National Immunization Program, CDC. Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR Recomm Rep* 2005;54(RR-14):10.

erythromycin is used, the estolate form is preferred because of its superior serum and respiratory tissue concentrations compared with the ethylsuccinate and stearate forms. Trimethoprim-sulfamethoxazole may be used as an alternative agent in rare clinical situations when macrolides are not tolerated, there is clear severe allergy to macrolides, or in cases of macrolide-resistant strains.

Treatment of infants with pertussis requires specific considerations. Infants younger than 6 weeks must be monitored for infantile hypertrophic pyloric stenosis (IHPS), which is associated with macrolide therapy, for 1 to 2 months after treatment. (35) Azithromycin is the preferred treatment because it seems to be less associated with IHPS than is erythromycin, although cases of IHPS have also been associated with azithromycin. (35)(36)(37) It must be stressed that the benefit of macrolide therapy outweighs the risk of IHPS, and such therapy should not be withheld for a young infant with pertussis. Trimethoprim-sulfamethoxazole is contraindicated in children younger than 2 months.

Supportive Care

Because antimicrobial therapy for pertussis may not be effective at the time of diagnosis, supportive care is the mainstay of management. Any infant younger than 6 months with suspected pertussis should be admitted to the hospital to monitor for progression of the illness and associated complications and to educate family members before discharge. (38) The duration of hospitalization depends on the clinical course, including the severity of cough episodes, ability to tolerate feeds, presence of apnea and bradycardia, and presence of other complications, such as pneumonia. Although cough may persist for weeks to months, the severity and frequency of these wane with time. Infants have an increased risk of mortality from pertussis, with 1 in 100 infants hospitalized for pertussis succumbing to the infection. (23)

Episodes of apnea may require mechanical ventilation. Infants with severe disease should be monitored for the development of pulmonary hypertension. (38) Patients with extreme leukocytosis may require exchange transfusion.

CONTROL MEASURES

Chemoprophylaxis

Postexposure chemoprophylaxis is recommended for asymptomatic close contacts and high-risk individuals. The CDC defines a close contact as "a person who had face-to-face exposure within 3 feet of a symptomatic patient; direct contact with respiratory, oral or nasal secretions; or shared the same confined space in close proximity with a symptomatic patient for ≥ 1 hour."(34) Chemoprophylaxis for high-risk individuals should be determined on a case-by-case basis. High-risk individuals include infants younger than 12 months, pregnant women in their third trimester, immunocompromised individuals, those with preexisting health conditions that may be worsened by pertussis, and individuals with close contact with high-risk individuals.

Chemoprophylaxis is most effective if given within the first 3 weeks after exposure and is recommended for all close contacts regardless of age or immunization status because previous immunization may not always prevent infection. Chemoprophylactic agents to be used, dosages, and duration of chemoprophylaxis are identical to the treatment regimens shown in Table 2. Any household contact of a patient with pertussis who is symptomatic should be treated as having pertussis.

Immunization

Immunization with a pertussis vaccine (DTaP or Tdap) is recommended for all exposed individuals who do not have an age-appropriate complete immunization history for pertussis.

Infection Prevention Measures

Droplet precautions are recommended for hospitalized patients with suspected or proven pertussis for 5 days after beginning therapy or for 21 days from initial coughing illness if no treatment was given.

Transporting of patients with proven or suspected pertussis in the ambulatory setting, such as from a pediatrician's office to a laboratory or radiology suite, should include communication among health-care workers regarding the appropriate use of droplet precautions.

Individuals exposed to a person with pertussis should be monitored for symptoms for up to 21 days. They should be excluded from child care facilities, school, and visitation at the hospital for 5 days after starting chemoprophylaxis or for 21 days if no treatment was given and they are not symptomatic.

PREVENTION

Vaccination is the primary method to prevent pertussis infections (Table 3). The specific composition of pertussis vaccines varies around the world, with some countries still using whole cell vaccines. In the United States, whole cell pertussis vaccine was initially introduced in the 1940s and was transitioned to only acellular vaccines for all recommended pertussis immunizations by 1997.

Primary Series

The current recommended schedule in the United States for pertussis vaccination is DTaP at 2, 4, and 6 months; 15 to 18 months; and 4 to 6 years of age; the fifth and final dose need not

TABLE 3. **Recommended Pertussis Vaccines**

PERTUSSIS-CONTAINING VACCINE RECOMMENDED	AGE
DTaP	2, 4, and 6 mo 15–18 mo 4–6 y
Tdap	7–10 y *(if incomplete vaccination prior)* 11–12 y Adults age ≥18 y *(once in place of tetanus booster)* Pregnant women *(once with each pregnancy)*

DTaP=diphtheria, tetanus, and acellular pertussis vaccine, Tdap=tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.
Based on Centers for Disease Control and Prevention Pertussis Vaccine Recommendations. Combination vaccines may be used for appropriate ages.

be given if the fourth dose was given at 4 years or older. Vaccine effectiveness after the primary series is 80% to 90%. (39)

Booster Doses

After the transition to DTaP, there was an increase in pertussis cases noted in 2005, especially in the cohort that received only DTaP and were approximately 5 years from their last dose (Fig 1). Findings in the US data mirrored findings in Australia after their transition to the acellular pertussis vaccine. (7) Based on these data, Tdap booster was recommended for 11- to 12-year-olds starting in 2005. Also, Tdap is recommended for any individual aged 7 to 10 years who has not previously been vaccinated or has been incompletely vaccinated with pertussis vaccine. (40)

Recommendations for Tdap vaccination have been expanded over the past several years based on changing epidemiologic data, including increased cases in infants younger than 12 months, which is associated with high mortality. Recommendations for booster doses for adults and pregnant women were made to address the issue of undiagnosed adult cases serving as a reservoir leading to severe infection in infants. In addition to the Tdap booster doses at 11 to 12 years old, all adults who have not previously received a Tdap should receive 1 dose of Tdap in place of routine tetanus vaccination. It is also recommended that pregnant women receive Tdap with each pregnancy at 26 to 37 weeks' gestation, ideally earlier during this period to allow for transfer of antibodies to the infant. (41) These recommendations are part of a cocooning strategy to prevent severe disease in young infants. This strategy uses vaccination of close contacts, such as parents, grandparents, and other caregivers, to help protect high-risk individuals. Although the cocooning strategy has been challenging, it is currently the best method available to protect infants who are too young to be vaccinated. (23)

Adverse Events and Contraindications

Local reactions to pertussis vaccines are the most common adverse events in infants after pertussis immunization and include erythema, swelling, and tenderness at the site of injection, and they are often accompanied by sleepiness, restlessness, vomiting, and low-grade fever. Entire limb swelling involving the thigh or the arm occurs in 2% to 3% of vaccines after the fourth or fifth dose of pertussis vaccine. Erythema, pain, and fever often occur in conjunction with the limb swelling, which resolves spontaneously and rarely limits a child's activity.

Systemic reactions to pertussis vaccination occur much less frequently after DTaP than after DTwP and include:

- Prolonged severe crying for 3 or more hours occurring within 48 hours of vaccination
- Seizures, most of which are febrile seizures
- Hypotonic-hyporesponsive episodes
- High fever (temperature ≥104.9°F [≥40.5°C])

Because these reactions do not result in any long-term sequelae, they are not contraindications to subsequent pertussis vaccination. (29)

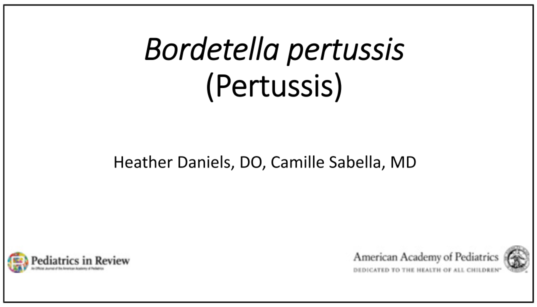
According to the American Academy of Pediatrics Committee on Infectious Diseases, the only true contraindications to pertussis vaccination include a previous anaphylactic reaction to a previous dose or a vaccine component, and an encephalopathy occurring within 7 days of a previous dose of pertussis-containing vaccine that is not attributable to another cause. (29)

Local events after pertussis vaccination in adolescents are common and include redness, swelling, and pain at the injection site. Severe arm swelling in this population is rare and self-limited. Systemic signs of illness, such as fever, headache, and fatigue, are common. Syncope is more common in adolescents than in infants and young children.

Summary

- Based on strong research evidence, the epidemiology of whooping cough is changing. (3)(5)
- Based on strong research evidence, many factors seem to be contributing to the changing epidemiology of pertussis, including the exclusive use of acellular pertussis vaccines, waning immunity, changes to the organism, vaccine refusal, and undiagnosed cases. (7)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)
- Symptoms of perioral cyanosis during coughing spells, posttussive emesis, and prolonged coughing illness all should raise concern for pertussis.
- Based on strong research evidence, although there has been an increase in incidence among children younger than 1 year and older than 10 years, the more severe complications are seen in infants younger than 6 months. (4)
- Based on some research evidence, early recognition of pertussis and appropriate antimicrobial therapy in infants may be associated with lower mortality. (33)
- Vaccination is the primary method to prevent pertussis; current immunization recommendations are based on changing epidemiology.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/5/247.supplemental.



Bordetella pertussis
(Pertussis)

Heather Daniels, DO, Camille Sabella, MD

Pediatrics in Review

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References and for this article are at http://pedsinreview.aappublications.org/content/39/5/247.

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1. A 7-week-old infant presents to your office with a history of cough for 4 days. The baby was born full term and without complications. There is no other significant medical history. The mother reports that overnight she noted several short episodes of apnea and is concerned that the baby has been feeding poorly. The baby is afebrile. There is a 5-year-old sibling in the home who has been healthy and has had all regularly recommended vaccinations. On further interview, the mother tells you that the maternal grandmother, who has been helping care for the infant, has had a "terrible" cough for the past 2 weeks with some posttussive emesis. The grandmother had received whole cell pertussis vaccine many years ago. What is the most likely epidemiologic factor leading to the transmission of pertussis to the infant in this scenario?
   A. Children aged 1 to 5 years are an important reservoir of pertussis infection.
   B. The acellular pertussis vaccine that is used now seems to be more effective than whole cell pertussis vaccine.
   C. There has been consistency in the *Bordetella pertussis* organism over time, leading to poor vaccine efficacy.
   D. There is waning immunity, leading to more transmission from adolescents and adults.
   E. Vaccine refusal has most likely contributed to the infant contracting pertussis.
2. A 3-month-old infant is brought to the emergency department after 6 days of cough, poor sleep, and some gagging with feeds. The parents also report some mild nasal congestion and coryza the week before development of the cough. The child has not yet received his 2-month vaccines. While being examined in the emergency department, the baby has a violent coughing episode and briefly becomes apneic, cyanotic, and limp but quickly recovers after approximately 20 seconds and begins to cry. You decide to admit the infant to the hospital for further evaluation and monitoring. What is the most common complication of this illness that you would be concerned about in this child?
   A. Encephalitis.
   B. Otitis media.
   C. Pneumonia.
   D. Pneumothorax.
   E. Rib fractures.
3. A 2-month-old infant presents to your office with a cough. The mother describes a recent upper respiratory tract illness without fever. She says that the cough started 4 days earlier, is paroxysmal in nature, with posttussive emesis and brief periods of apnea. You are concerned for pertussis infection. What is the best method of diagnosis of *B pertussis*?
   A. Direct fluorescent antibody testing.
   B. Rapid antigen testing.
   C. Respiratory culture.
   D. Polymerase chain reaction testing.
   E. Serologic testing.
4. An infant is hospitalized with confirmed pertussis infection, and macrolide therapy is initiated. There are 2 other siblings in the home, ages 3 and 6 years, who are both up to date with their vaccinations, including pertussis. The parents are concerned about the other children in the home becoming ill. What would you recommend for the siblings at this time?
   A. An immediate booster vaccine with diphtheria, tetanus, and acellular pertussis vaccine (DTaP) is recommended for both siblings.
   B. Begin macrolide therapy for both siblings and any other household contacts.

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C. No chemoprophylaxis treatment is necessary because the siblings have both been vaccinated.
D. Test both siblings for *B pertussis* infection, and if the test result is positive, begin chemoprophylaxis.
E. Vaccination with DTaP is recommended for the siblings if they are considered high risk.

5. An 8-year-old who recently immigrated to the United States from Guatemala has not received all the recommended US vaccinations. In addition to other catch-up vaccines, what is the current recommendation for the child in terms of pertussis vaccination?

A. A DTaP is indicated at this time.
B. A tetanus and diphtheria (Td) vaccine is indicated at this time.
C. A tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine is indicated at this time.
D. Both a Td and a DTaP are indicated at this time.
E. Pertussis vaccine alone is indicated.

Index of Suspicion

1 Concurrent Upper Respiratory Tract Infection and Vulvar Ulcers in a Teenage Girl

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Chu, Genisca, and Kaziny have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old previously healthy white girl presents to the emergency department (ED) with 6 days of worsening cough and sore throat, 5 days of fever (highest temperature 102.5°F [39.2°C]), and painful red papules that have progressed to deep ulcers on her labia minora (Fig 1). The sores are painful to the touch, with worse pain during urination. The patient denies sexual activity, urinary frequency or urgency, pruritus, or hematuria. The last time she shaved her genital region was several months earlier. At symptom onset, she had several episodes of dizziness, with standing as well as nonbilious, nonbloody emesis, which have now resolved. Acetaminophen and ibuprofen have been given for fever. Miconazole and zinc oxide creams were used for the vulvar symptoms and did not help. She saw her primary pediatrician 2 days ago and a laboratory evaluation was performed, but the parents do not know the results.

On arrival at the ED the patient's temperature is 98.4°F (36.9°C), blood pressure is 106/65 mm Hg, heart rate is 111 beats/min, and respiratory rate is 16 breaths/min. Her genitourinary examination reveals 3 deep ulcers with ragged edges and clean bases just lateral to the right labia near the introitus that are painful to the touch. No erythema or inflammation of the labia or surrounding region is noted. The remainder of her physical examination findings are normal.

Review of the electronic medical record showed that the patient's pediatrician had tested her via the rapid influenza diagnostic test, rapid strep test, and spot test for infectious mononucleosis, all of which had negative results. The pediatrician also tested for *Candida, Trichomonas,* and bacterial vaginosis via a genital swab; these were negative as well.

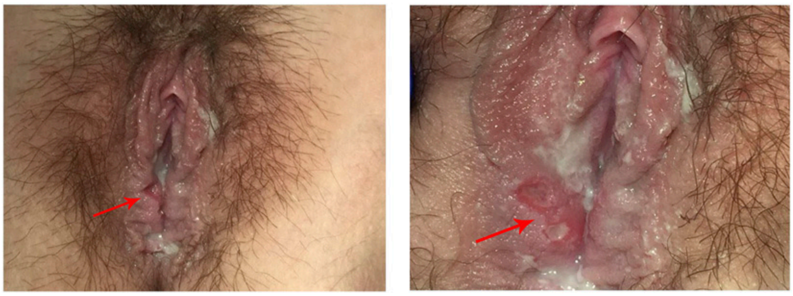

Figure 1. Photographs of the patient's initial genitourinary examination. Red arrows indicate the ulcerative lesions.

In the ED the patient tested negative for gonorrhea and chlamydia by urine polymerase chain reaction (PCR), herpes simplex virus (HSV) by serum PCR and by genital swab quantitative PCR, and syphilis by treponemal antibody. A wound culture taken from the base of 1 of the ulcers grew abundant mixed urogenital flora. A fungus culture from the vaginal discharge was negative. Of note, the patient's Epstein-Barr virus (EBV) antibody panel results were as follows: immunoglobulin (Ig) M, less than 10 U/mL; IgG, 483 U/mL (<18 U/mL negative); and EBV nuclear antigen, 134 U/mL (<18 U/mL negative), indicating that the patient had been infected with EBV in the past but did not have an active infection at this time. The characteristics of the ulcers combined with the negative laboratory results confirmed the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/5/258.

DISCUSSION

The Condition

Lipschütz ulcers are also referred to as acute genital ulcers, acute vulvar ulcers, primary aphthous ulcers, and ulcus vulvae acutum. They were first described in a case series by Benjamin Lipschütz, a dermatologist and microbiologist, in 1913. (1) To this day they remain a relatively rare and unknown condition, and few cases are published in the pediatric literature. These ulcers present as exquisitely painful, well-defined lesions with a necrotic base on the labia majora, labia minora, perineum, or lower vagina or at the introitus. Ulcers can be single or multiple. Dysuria is usually present, although other symptoms of a urinary tract infection are absent. The typical patient is a prepubertal or pubertal teenage girl, often without any sexual history, who also presents with symptoms of an upper respiratory tract infection (fever, malaise, pharyngitis, tonsillitis, lymphadenopathy, myalgias, headache, cough, congestion). (2)(3)(4)(5) The youngest patient reported in the literature was 17 months old at the time of diagnosis; (6) multiple case reports detail this diagnosis in adult women as well. (2) The condition is most commonly associated with EBV, although case reports have also implicated cytomegalovirus, *Mycoplasma, Parvovirus, Salmonella typhi,* and mumps. (2)(7) Often, no infectious etiology is identified.

The pathophysiology of Lipschütz ulcer is unknown. One possibility is that EBV infects the B lymphocytes, which then circulate throughout the body, causing a direct cytotoxic effect in the epithelial cells of the genital tract. (3)(4) Alternatively, the condition may be due to immune complex formation secondary to a hypersensitivity reaction to a viral or bacterial infection, with deposition of immune complexes leading to microthrombosis and necrosis at sites distant from the original infection. (2)

Diagnosis

The differential diagnosis of a prepubertal or pubertal teenage girl presenting with vulvar ulcers includes sexually transmitted diseases (STDs), specifically HSV. A detailed sexual history is warranted, as well as STD testing, to rule out any treatable causes. At minimum, testing for HSV is indicated, and testing for other STDs may be performed based on history and physical examination findings. Furthermore, a careful history and thorough examination evaluating for autoimmune causes of genital ulcers, including Behçet disease, Crohn disease, and pyoderma gangrenosum, must be performed. In the setting of negative STD test results, low suspicion for autoimmune disease, and concurrent symptoms of upper respiratory tract infection, a diagnosis of Lipschütz ulcers can be made. Biopsy of the ulcer is not recommended if clinical suspicion for Lipschütz is high because pathology findings are nonspecific and the procedure, thus, inflicts pain to the patient with no evident benefit.

Management and Patient Outcome

The patient was discharged from the ED with lidocaine jelly for symptomatic relief. A phone call was made to the patient's home 1 month after her ED visit. The patient's outcome was discussed with her father, who stated that the lidocaine jelly provided relief for the ulcer pain. The ulcers slowly shrank in size and then eventually resolved over the 2 to 3 weeks after her ED visit. Her cough persisted for 3 to 4 weeks and was symptomatically relieved with an over-the-counter cough syrup. The patient is now well and back to her baseline.

Lessons for the Clinician

- Lipschütz ulcer should be on the differential diagnosis of a teenage girl who presents with vulvar ulcers, especially in the presence of a concurrent upper respiratory tract infection.
- A thorough history and physical examination should be performed to evaluate for sexually transmitted and autoimmune diseases. Laboratory evaluation is left to clinical suspicion, but herpes simplex virus testing is recommended. A biopsy is not necessary.
- Ulcers resolve spontaneously within 2 to 3 weeks, and only supportive therapies are needed.

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2 Sore Throat and Dysphagia in a 6-year-old Boy

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AUTHOR DISCLOSURE Dr Belfer has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy, fully vaccinated 6-year-old boy presents to the emergency department with sore throat and difficulty swallowing starting the previous evening. That morning the boy had complained of difficulty swallowing when eating breakfast and was noted to have some drooling. He was given acetaminophen before presenting to the emergency department. The boy has a history of enlarged tonsils, but no other pertinent medical history.

At presentation, he is febrile (102.7°F [39.3°C]), with a heart rate of 151 beats/min, respiratory rate of 20 breaths/min, blood pressure of 109/63 mm Hg, and oxygen saturation of 99% on room air. On physical examination the boy is noted to be ill appearing, with enlarged and erythematous tonsils. Neck examination is significant for tenderness on the lateral aspects bilaterally, with lymphadenopathy of ~2 cm noted on the left and right sides of the neck. There is no stridor or voice change, and the boy has clear breath sounds bilaterally on auscultation. His neck is observed to be supple, with no restriction in range of movement.

Laboratory studies reveal a white blood cell count of 34,000/mL, with 94% neutrophils on the differential cell count. A metabolic panel shows a bicarbonate level of 18 mEq/L (18 mmol/L) but is otherwise normal. Uric acid and lactate dehydrogenase levels are normal. Results of a respiratory viral panel, rapid strep test, and infectious mononucleosis screen are negative.

Imaging revealed the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/5/260.

DISCUSSION

Lateral neck radiography was performed and revealed an enlarged epiglottis, concerning for epiglottitis. The patient was given ceftriaxone and dexamethasone, and airway management was immediately instituted. The patient was observed to be very comfortable and in no acute respiratory distress, so a bedside fiberoptic endoscopy was performed by ear, nose, and throat (ENT) specialists. Airway visualization revealed erythema and mild edema of the epiglottis, aryepiglottic folds, and arytenoid cartilages. The airway was observed to be widely patent. The findings confirmed a diagnosis of epiglottitis. The boy was admitted to the hospital and observed on continuous pulse oximetry on the general medicine inpatient floor. Although most children with epiglottitis are admitted to the ICU, the child was deemed to be stable enough from a respiratory standpoint for general medicine floor admission. Ceftriaxone and dexamethasone use were continued. The boy remained stable, with no respiratory distress, and tolerated a normal diet with resolution of his dysphagia. His blood culture grew *Haemophilus influenzae* serotype A at 19 hours of incubation. Follow-up blood cultures the following 2 days showed no growth. The boy was discharged after 2 days and was prescribed cefdinir to complete a total of 10 days of antibiotic drug therapy.

The Condition

Although the incidence of epiglottitis has greatly decreased since the advent of the *H influenzae* type b vaccine, it is a condition that can be quickly fatal when not included on a differential diagnosis. Anatomically, the epiglottis and the bordering arytenoid cartilages create the opening of the larynx. In epiglottitis, a cellulitis of these structures causes inflammation and edema, with the resulting enlargement of the epiglottis creating a risk for obstruction of the airway.

Children with epiglottitis often appear toxic, with rapidly progressive symptoms that can include sore throat, dysphagia, and high fevers. Ultimately, respiratory failure due to obstruction of the airway is responsible for mortality from the condition. Although respiratory distress can be an early or late symptom, children with a partially obstructed airway exhibit the classic “tripod” position: leaning forward while supporting themselves with their arms. Drooling and voice changes can be seen in epiglottitis as well.

Clinically, providers must have a low threshold of suspicion for the diagnosis as a result of the potentially quick progression of disease. Protecting the airway should be the clinician’s top priority, and, therefore, diagnostic evaluation must be weighed against the risk of delaying treatment. Although laryngoscopy can ultimately confirm the diagnosis, it should be performed only if the patient is clinically stable. If performed, an environment in which the airway can be quickly secured (via intubation or tracheostomy), such as an operating room or an intensive care setting, is strongly recommended. Similarly, imaging should be considered only when the clinical presentation is ambiguous and should be performed only in stable patients. If imaging is performed, the patient should preferably be accompanied by a physician skilled in airway management (ie, an anesthesiologist, intensivist, ENT specialist, or emergency physician) and should be given priority to have the imaging performed in a timely manner. Lateral radiographs show the classic “thumb sign” of the enlarged and edematous epiglottis. (1)

The creation of the *H influenzae* type b vaccine in the mid-1980s has greatly affected the epidemiology of the resulting diseases, including epiglottitis. Most *H influenzae*–caused infections were seen in children younger than 2 years, with more than 90% of cases seen in children younger than 5 years. In this age group, the annual incidence was estimated to be up to 129 cases per 100,000 children. The incidence has significantly decreased since the vaccine was created, with invasive *H influenzae*–caused disease in the United States currently causing only up to 1 case per 100,000 children younger than 5 years. (2)

With the addition of the *H influenzae* type b vaccine to the standard immunization schedule, the mean age of epiglottitis saw an increase. One study from Boston found a mean age increase of almost 6 years, from 5.8 to 11.6 years old. (3) Similarly, a British study observed a decrease in epiglottis cases in the population younger than 15 years, with a resulting increase in an older population. (4)

Other causes of upper airway obstruction must be included in a differential diagnosis with epiglottitis. Peritonsillar and retropharyngeal abscesses were consider by the clinicians in this case and can present similarly to epiglottitis, with fevers, drooling, and restricted neck movement. A lateral neck radiograph, performed to diagnose the patient described herein, can be used in the diagnostic evaluation of these conditions. Foreign bodies and congenital anomalies of the upper airway can cause blockage of the airway, but both are usually seen in afebrile children. Although anatomically similar to epiglottitis, an enlarged epiglottis can be caused by trauma, thermal injury, and even radiation to the neck.

The boy in this case came into the emergency department with an atypical, yet much less quickly progressive, presentation of epiglottitis. Although clinically stable, the evolving neck pain with continued fevers suggested to the medical team the possibility of a more serious illness.

Fortunately, he was initiated on antibiotic drug therapy soon enough to prevent a potentially fatal progression of the infection. High suspicion with a low threshold to treat remained true in this case as important clinical pearls in diagnosing and treating epiglottitis.

Lessons for the Clinician

- Epiglottitis must be considered in the differential diagnosis for a patient with sore throat and dysphagia because it can be quickly fatal if untreated.
- The condition should be considered regardless of a patient's vaccination status.
- The age at presentation of epiglottitis has increased since the advent of the *Haemophilus influenza* type b vaccine.
- Most patients with epiglottitis should be cared for in an intensive care setting owing to fear of impending respiratory failure.

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3

Persistent Respiratory Distress in a Teenager Treated for Severe Asthma Exacerbation

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AUTHOR DISCLOSURE Drs Shieh and Siddaiah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 15-year-old girl with severe persistent asthma presents to the emergency department with acute respiratory distress. Her common triggers are environmental allergens, predominantly dogs and cats. Her asthma had been fairly controlled with her current home regimen, which included daily fluticasone/salmeterol 230/21 μg 2 puffs twice daily, montelukast 5 mg once daily, loratadine, and as-needed albuterol until she was recently exposed to dogs. She experiences a cough, becomes dyspneic, and uses her rescue inhalers, which fail to provide relief.

On presentation, her vital signs are significant for a heart rate of 124 beats/min and a respiratory rate of 28 breaths/min. She requires oxygen therapy to achieve oxygen saturation of 98%. The physical examination reveals that she is leaning forward in the tripod position and using accessory muscles to breathe. She is unable to speak full sentences without feeling short of breath. Her lungs have significantly decreased breath sounds, with occasional wheezing heard throughout her lung fields. No stridor is present. There is no cyanosis in her extremities. A portable chest radiograph reveals hyperexpansion with prominent central lung markings and peribronchial cuffing consistent with reactive airway disease.

She is immediately treated with subcutaneous epinephrine, nebulized albuterol, nebulized ipratropium, and intravenous methylprednisolone. Because of poor response, she receives intravenous magnesium sulfate and intravenous aminophylline. Results of polymerase chain reaction testing for nine common viral respiratory pathogens are negative. Due to increasing dyspnea requiring oxygen therapy, she is transferred to the ICU, where she requires treatment with continuous albuterol and systemic corticosteroids. On day 3, she no longer requires continuous albuterol. Due to intermittent respiratory distress with poor air movement and stridor, she is treated with continuous albuterol and heliox on day 6. A minimally invasive bedside tool confirms her diagnosis, and she is discharged 2 days later.

The Case Discussion, References, and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/5/261.

DISCUSSION

According to the National Institutes of Health, (1) treatment for an asthma exacerbation should be initiated immediately. Supplemental oxygen should be started to correct hypoxemia. Patients should be treated with repetitive or continuous short-acting $\beta 2$-agonist with the addition of inhaled ipratropium bromide in severe cases. Oral corticosteroids should be given to patients with moderate or severe exacerbations or patients who fail to respond to initial treatment to reduce airway inflammation. Adjunctive treatments, such as intravenous magnesium sulfate or heliox, should be considered in patients who are unresponsive to treatment. Response to treatment can be monitored with pulse oximetry, clinical symptoms, and physical examination.

Differential Diagnosis

If a patient with presumed asthma exacerbation does not respond to bronchodilator treatment, alternative diagnoses must be considered. Patients with anaphylaxis present with respiratory distress and frequently have skin findings, including flushing, urticaria, and angioedema. Epiglottitis is characterized by an abrupt onset of high fever, with drooling, dysphagia, and sore throat. Patients with airway compromise due to foreign body obstruction present with tachypnea, tachycardia, or stridor. These patients may rapidly deteriorate if swelling or bleeding occurs in the airway. Patients with laryngeal abnormalities, including polyps or cysts, causing obstruction have symptoms such as hoarseness, change in voice quality, and increased effort in voice production.

The Condition

Vocal cord dysfunction (VCD), also known as paradoxical vocal fold motion, can mimic an asthma exasperation. The incidence of VCD in pediatric patients is unknown. However, the study by Powell et al (2) reported that VCD mainly affects adolescents and is more prevalent in girls. It is believed to have similar triggers as asthma, including cold air, allergies, and exercise. Other triggers for VCD include viral upper respiratory tract infections, gastroesophageal reflux disease, or psychological stresses. Patients with VCD may experience dyspnea, tightness in the throat, or nonproductive cough. Stridor may be heard and is usually loudest in the anterior neck. It is difficult to distinguish VCD from asthma because both conditions have similar symptoms, and patients may actually have both conditions.

Diagnosis

To definitively diagnose VCD, direct visualization through a laryngoscope of inappropriate adduction of the vocal cords with posterior chinking during inspiration or both inspiration and expiration is required. As a result of this obstruction, the patient experiences wheezing or stridor over the larynx, which can be conducted to the lower lung fields. It is difficult to diagnose VCD in an asymptomatic patient because the vocal cords show normal movement, and most patients will have normal pulmonary function studies. However, when symptomatic, patients in a report by Niggemann et al (3) had a truncated inspiratory segment with blunting of the expiratory limb of flow volume curves. A normal flow volume curve in a symptomatic patient does not rule out VCD. Occasionally, symptoms can be triggered during an exercise challenge study, methacholine challenge study, or hyperventilation.

After a prolonged hospital course, slow clinical improvement with intermittent stridor, and poor response to albuterol, a bedside examination with a flexible fiberoptic laryngoscope is performed on this patient, which reveals paradoxical vocal cord movement during hyperventilation.

Management

The goal of immediate treatment is to stop the attack. Breathing techniques to relax the throat or exhaling through pursed lips helps counteract the closure of the respiratory tract. Some techniques to open vocal cords include panting with the tongue extruded, diaphragmatic breathing, and taking rapid deep inspirations. In severe cases, positive pressure ventilation forces air through the narrowed opening formed by the adducted cords. Previous reports, such as that by Reisner and Borish, (4) demonstrate that a mixture of helium and oxygen (heliox) is effective in relieving symptoms. Endotracheal intubation or permanent tracheostomies may be required in severe cases.

The mainstay for long-term management of VCD includes laryngeal control therapy and psychotherapy during asymptomatic periods. Such speech therapy includes techniques for voice control, sip and swallow routines, and breathing exercises that use the diaphragm to relax the vocal cords. Concurrently, psychotherapies have been used to reduce stress and anxiety. In a study of adults by Varney et al, (5) insomnia, anxiety, and stress were associated with VCD, and low-dose amitriptyline was shown to be effective to treat patients. Patients should remain aware of precipitating triggers and identify onset of symptoms quickly. Other triggers of asthma should be controlled to minimize a component of a reactive airway.

Clinical Course

She was treated with heliox, and her symptoms improved significantly. The following exercises were used to relax the vocal cords and focus on diaphragmatic breathing:

- Place a book on the abdomen to increase awareness of abdominal movement while breathing.
- Sniff in through the nose slowly and gently exhale through pursed lips.
- Make the *s* or *sh* sound during exhalation.
- Inhale and exhale deeply and slowly.
- Pant quickly in and out of the nose to feel movement of the diaphragm.

She was discharged, and no adjustments were made to her home medications.

Lessons for the Clinician

- An astute clinician must consider vocal cord dysfunction (VCD) in patients who do not show response to nebulized treatment or who require multiple hospital visits despite taking large doses of medications for asthma.
- Diagnosis of VCD is confirmed by visualization of adduction or posterior chinking of vocal cords through a fiberoptic laryngoscope.
- Breathing techniques to relax the throat or counteract the closure of the vocal cords is effective to manage VCD, and positive pressure ventilation with heliox is effective in severe cases.
- Speech therapy is effective for long-term management of VCD to relax the vocal cords.
- In patients with VCD and underlying asthma, proper diagnosis of VCD can decrease exposure to inhaled corticosteroids, reduce unnecessary adjustments to medications, and reduce adverse effects from systemic therapy.

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4 Muscle Rigidity in a 5-year-old Boy

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AUTHOR DISCLOSURE Drs Ference, Paprocki, Boyd, Butler, and Bratcher have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy, unimmunized 5-year-old boy is found to have apnea, muscle rigidity, and trismus when paramedics arrive at his home. He has severe arching of his back, with only his head and buttocks touching the gurney. Symptoms began with an intermittent dry cough and worsening dysphagia 2 days ago. He has no history of fevers, vomiting, diarrhea, or headache. His family denies any recent medication exposures, wounds, or direct contact with animals or insects. He is intubated for respiratory failure but continues to have episodes of jaw clenching associated with bradycardia and desaturations. He is admitted to the PICU for further evaluation and management.

On admission, he continues to have episodes of muscle spasm and spinal rigidity despite increasing dosing of continuous dexmedetomidine, fentanyl, and midazolam. The initial examination reveals a normal electrolyte panel, blood calcium level, C-reactive protein level, complete blood cell count, and head computed tomographic scan. His cerebrospinal fluid shows a white blood cell count of 2/μL (<.01×10^9/L), a glucose level of 96 mg/dL (5.3 mmol/L), and a protein level of 0.021 g/dL (0.21 g/L). He is started on empirical antibiotic treatment with vancomycin, ceftriaxone, and metronidazole. Results of further testing, including cerebrospinal fluid enterovirus, varicella, and herpes simplex virus polymerase chain reactions; a comprehensive drug screen; magnetic resonance imaging of the head/neck/spine; and strychnine testing, return negative. Continuous video electroencephalography (EEG) to rule out underlying seizure activity supported the eventual diagnosis.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/5/262.

DISCUSSION

During hospital admission, the patient continued to have severe muscle spasms and trismus to the point of dislodging 2 upper incisors after clamping down on his endotracheal tube. Along with his rigidity, he was noted to have autonomic instability with bradycardia, tachycardia, hypertension, and desaturations. He had several episodes of severe chest wall rigidity and laryngospasm, inhibiting effective bag-mask ventilation despite intubation. Continuous video EEG revealed continuous muscle contraction concerning for dystonia versus tetany. Based on his clinical status and EEG findings, he was diagnosed as having tetanus due to an unknown source.

The Condition

Tetanus is an acute paralytic illness caused by *Clostridium tetani,* a gram-positive, anaerobic, spore-forming bacillus found in soil and animal intestinal tracts. Infection is rare in the United States, with fewer than 40 confirmed cases reported to the Centers for Disease Control and Prevention (CDC) each year. Most cases occur in the setting of no vaccination, inadequate vaccination, or inadequate wound care. An obvious contaminated wound is seen in most cases, but in approximately 5% no wound is noted. The case-fatality rate in the United States from 2001 through 2008 was 13.2%.

Clostridium tetani produces the exotoxin tetanospasmin, which acts in the central nervous system by irreversibly blocking inhibitory glycine and γ-aminobutyric acid–releasing neurons. This results in the clinical manifestations of tetanus, including trismus (lockjaw), risus sardonicus (sardonic smile with facial and buccal spasm), and opisthotonos (extreme body hyperextension). Other symptoms include dysphagia, irritability, and pharyngeal/laryngeal spasm. The clinical triad of rigidity, muscle spasms, and autonomic dysfunction can lead to severe pain, fractures, respiratory failure, and acute cardiac death. Diagnosis is generally made based on clinical findings. Often, *C tetani* is difficult to isolate in culture; therefore, negative culture results do not rule out the diagnosis. Although EEG was used in the present patient, this is not necessary for diagnosis. Other diagnoses to consider include rabies, trismus from dental or retropharyngeal abscess, hypocalcemia, dystonic drug reaction, seizure, and strychnine poisoning.

Management

The mainstay of treatment is supportive care with emphasis on maintaining airway patency. Sedation and neuromuscular blockade are commonly required to manage rigidity and spasms. Metronidazole and tetanus immune globulin (TIG) are recommended as primary tetanus therapy. When autonomic dysfunction is present, treatment with magnesium sulfate and/or β-blockade may be beneficial. Additional supportive measures include close monitoring of the patient's hemodynamics, providing nutrition (high metabolic demand from increased muscular activity), and limiting environmental stimuli. Recovery depends on regeneration of new neuron synapses to restore muscle relaxation.

Prevention

Prevention strategies of tetanus can be divided into 3 categories: primary, secondary, and tertiary. Primary prevention is given with tetanus vaccine: 3 doses in the first year, a fourth dose at 15 to 18 months, and a fifth dose between 4 and 6 years. A booster vaccine should then be given every 10 years. Secondary prevention includes use of TIG and a tetanus vaccine for wounds that are at risk for contraction of tetanus. Patients at risk include those who are not fully immunized or who have a severe cut, dirty wound, or burn. Tertiary prevention is achieved with a tetanus vaccine at the time of infection, as having tetanus does not confer immunity. Vaccine adverse effects include pain, redness, or swelling at the injection site, and rarely an Arthus reaction. Contraindications include anaphylaxis to a previous dose of this vaccine, severe allergy to a vaccine component, coma, or repeated seizures within 7 days of receiving the vaccine.

Clinical Course

The patient ultimately required neuromuscular blockade with continuous vecuronium infusion, treatment with baclofen and dantrolene, and tracheostomy placement. He was treated with human TIG and 14 days of metronidazole. He was slowly weaned off all of his medications, decannulated, and discharged on hospital day 26. Before discharge, he received his first tetanus vaccination.

Lessons for the Clinician

- Tetanus is a rare but potentially deadly condition related to the exotoxin tetanospasmin produced by *Clostridium tetani*.
- Clinical symptoms include trismus (lockjaw), risus sardonicus (sardonic smile with facial and buccal spasm), opisthotonos (extreme body hyperextension), dysphagia, irritability, and pharyngeal/laryngeal spasm.
- The clinical triad of rigidity, muscle spasms, and autonomic dysfunction can lead to severe pain, fractures, respiratory failure, and acute cardiac death.

- The diagnosis of tetanus is made based on clinical findings and a history suggestive of possible tetanus exposure and/or inadequate immunization.
- Treatment includes metronidazole, tetanus immune globulin, and supportive care measures to ensure airway patency and treat muscle rigidity and spasm.

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5

Abdominal Distention, Poor Growth, and Motor Delay in a 1-year-old Girl

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AUTHOR DISCLOSURE Dr McCarthy has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 1-year-old girl presents to the pediatrician's office with an enlarging abdomen since birth, poor weight gain since 6 months of age despite eating well, and developmental delay. She does not crawl or pull to stand and is unable to support herself on all fours for more than a few seconds. She was born at full term after an unremarkable pregnancy. She required a 3-day stay in the NICU for management of hypoglycemia, which resolved before discharge. She takes no medications and is up to date on immunizations.

At presentation she is afebrile and her heart rate is 122 beats/min, respiratory rate is 45 breaths/min, and oxygen saturation is 100% on room air. She is 26.2 in tall (66.5 cm, <1st percentile) and weighs 17.68 lb (8.02 kg, 17th percentile). She is tachypneic but appears comfortable, and lung sounds are clear. Her abdomen is protuberant and firm, and it is difficult to palpate the edge of the liver. Her legs are thin, with decreased strength and tone. She has normal verbal and fine motor skills for her age but has gross motor delays as described previously.

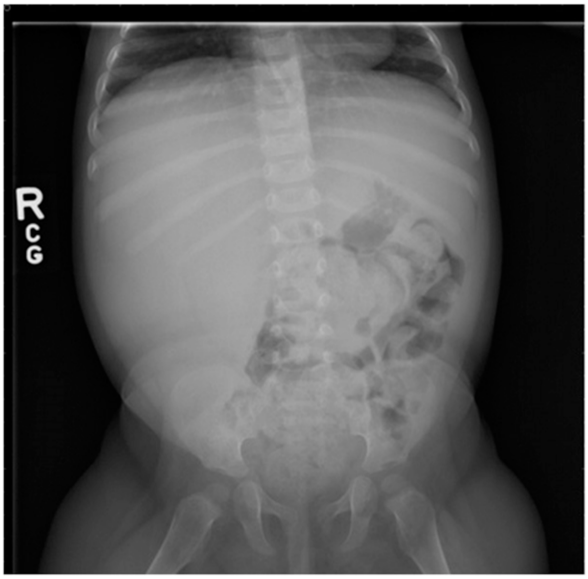

Figure. Abdominal plain radiograph showing hepatomegaly and centrally displaced loops of bowel.

Initial evaluation includes a chest radiograph, which is negative for any acute cardiopulmonary process but shows low lung volumes. Abdominal radiography reveals a markedly enlarged liver with the tip projecting over the right iliac crest (Fig).

Serum chemistry values are notable for sodium of 136 mEq/L (136 mmol/L), potassium of 4.1 mEq/L (4.1 mmol/L), chloride of 98 mEq/L (98 mmol/L), bicarbonate of 11 mEq/L (11 mmol/L), glucose less than 20 mg/dL (<1.1 mmol/L), and lactic acid of 109 mg/dL (12.1 mmol/L). She is admitted to the hospital for management of severe hypoglycemia.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/5/263.

DISCUSSION

Based on the constellation of hepatomegaly, hypoglycemia, lactic acidosis, hypertriglyceridemia, hyperuricemia, and failure to thrive, a diagnosis of glycogen storage disease (GSD) is made on clinical grounds. Genetic testing confirms the diagnosis of GSD type Ib.

Condition

Glycogen storage disease type I is an autosomal recessive disorder with an estimated prevalence of 1 in 100,000. Deficiencies in glucose-6-phosphatase (type Ia) or gluose-6-phosphate translocase (type Ib) block both glycogenolysis and gluconeogenesis, leading to hypoglycemia and the accumulation of fat and glycogen in the liver and kidneys. Patients are at risk for sudden death due to hypoglycemia when fasting. The combination of hepatomegaly and hypoglycemia should lead the clinician to suspect GSD, particularly types 0, I, III, VI, and IX.

Patients with GSD I have a characteristic appearance with a doll-like face, plump cheeks, thin extremities, short stature, and a protuberant abdomen. Hepatomegaly and hypoglycemia typically develop at 3 to 6 months, although some newborns may have hypoglycemic episodes. After a meal, patients are often able to maintain their blood glucose levels for 2 to 4 hours, which can complicate the detection of hypoglycemia in infants who feed frequently.

Long-term complications of GSD I include short stature, osteoporosis, delayed puberty, chronic kidney disease, hypertriglyceridemia-induced pancreatitis, gout, and the development of hepatic adenomas that can undergo malignant transformation. Patients with GSD Ib have the additional risk of recurrent infections due to neutropenia and an increased incidence of inflammatory bowel disease and autoimmune hypothyroidism.

Diagnosis

The diagnosis of GSD I is confirmed either by detection of characteristic gene abnormalities or by liver biopsy with testing for glucose-6-phosphatase and glucose-6-phosphate translocase activity. After diagnosis, complete blood cell count, lipid profile, vitamin D level, platelet function assay, uric acid level, and liver and kidney imaging are all recommended to evaluate for associated complications and determine baseline levels. Siblings of the affected child should be evaluated as early as possible to avoid delays in treatment.

Treatment

Treatment of GSD I is primarily focused on dietary management to maintain adequate blood glucose, and a metabolic nutritionist should be consulted soon after the diagnosis. Frequent small meals that are high in complex carbohydrates and supplementation with uncooked cornstarch help provide a steady, slow-release source of glucose. Patients should also avoid fructose and sucrose and limit their intake of lactose and galactose. Appropriate nutrition mitigates many of the metabolic abnormalities and long-term sequelae of GSD I, although patients may still require treatment for gout, dyslipidemia, hypertension, and other complications. Liver transplant provides enzyme replacement and prevents lethal hypoglycemic episodes but does not address other affected organ systems. Patients must continue a modified diet, and many still go on to require renal transplant. Liver transplant is typically delayed as long as possible due to the potential for surgical complications.

Prognosis

With proper treatment, most affected individuals live to adulthood. Neurocognitive outcomes depend on the number of hypoglycemic episodes. Regular surveillance for osteoporosis, anemia, chronic kidney disease, dyslipidemia, and hepatic adenomas is recommended to ensure early recognition and intervention.

Lessons for the Clinician

- Glycogen storage disease (GSD) should be suspected in patients with hypoglycemia, hepatomegaly, and poor growth.
- Treatment of GSD I is focused on providing appropriate nutrition.
- Liver transplant prevents lethal hypoglycemia but has a high risk of complications.
- With proper treatment and surveillance, patients with GSD I have a good overall prognosis.

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6

Seizures and Low Cerebrospinal Fluid Glucose in a 4-day-old Boy

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AUTHOR DISCLOSURE Drs Belal and Chandra have disclosed no financial relationships relevant to this article. Dr Day-Salvatore has disclosed that she has research grant funding for registries and clinical trials from Sanofi Genzyme related to lysosomal storage diseases. She also serves as a lysosomal storage disease expert for Sanofi Genzyme and receives travel reimbursement and honoraria from the company. Dr Belal's current affiliation is Mount Washington Pediatric Hospital, Baltimore, MD. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 38-week, appropriate-for-gestational age boy born to a 31-year-old primagravida mother and a 36-year-old father by emergency cesarean delivery due to failure-to-progress and fetal distress 26 hours after spontaneous rupture of membranes with clear amniotic fluid is admitted electively to the NICU for possible severe bacterial infection as the mother developed an intrapartum fever. Pregnancy was normal. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. There were no reported exposures to tobacco, alcohol, or drugs. The newborn is asymptomatic on admission. His birthweight is 3,070 g (40th percentile), length is 51 cm (80th percentile), and head circumference is 32.5 cm (20th percentile). His temperature is 98.6°F (37°C), heart rate is 130 beats/min, respirations are 40 breaths/min, oxygen saturation is 99% on room air, and blood pressure is 69/34 mm Hg. Physical examination is notable only for a small right preauricular tag. He shows no dysmorphic features; anterior fontanelle is flat and patent; red reflex is present bilaterally; chest is clear to auscultation; heart sounds are normal, with no clicks, murmurs, or gallops; abdomen is lax, with no palpable organs or masses; both testicles are descended in the scrotum; and Tanner stage is 1. No rashes, lesions, or birthmarks are noted on the skin, and primitive reflexes are present.

The child receives ampicillin and gentamicin for 48 hours. Blood culture results are negative. On day 4, the newborn starts to have feeding intolerance that progresses to episodes of apnea, desaturations, and eye rolling, with "arm bicycling"–like movements. A repeated evaluation for possible sepsis is initiated. Antibiotics are started again, along with acyclovir. Results of brain computed tomographic scanning and magnetic resonance imaging are normal. Cerebrospinal fluid (CSF) and blood cultures and CSF herpes simplex virus polymerase chain reaction return negative. Complete blood cell count, C-reactive protein level, serum ammonia level, bicarbonate level, electrolyte levels, and results of state newborn screening are all normal. The CSF analysis shows a white blood cell count of 3/μL (<.001×10^9/L), no red blood cells, a protein level of 0.1 g/dL (1 g/L), and a glucose level of 34 mg/dL (1.9 mmol/L), along with a serum glucose level of 87 mg/dL (4.8 mmol/L). A video electroencephalogram captures multiple seizure episodes. Leviteracetam and phenytoin treatment is initiated. Lumbar puncture repeated after 4 hours of fasting shows a CSF glucose level of 30 mg/dL (1.7 mmol/L) along with a serum glucose level of 95 mg/dL (5.3 mmol/L) at the time of the spinal tap in the absence of red or white blood cells. The newborn continues to have seizures despite taking antiepileptics. Further family history obtained is remarkable for history of seizures in the patient's mother during childhood and a seizure disorder in the maternal aunt and her son. Due to low CSF glucose level–associated seizures with a concomitant normal serum glucose level, a specific genetic disorder is suspected. Additional genetic testing confirms the diagnosis. A special diet results in termination of the seizures.

The Case Discussion and Suggested Readings appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/5/265

DISCUSSION

SLC2A1 gene sequencing revealed heterozygosity for a missense mutation resulting in substitution of glycine for arginine at amino acid position 153, which the laboratory classified as a variant of unknown significance. However, 2 other variants altering this specific amino acid have been reported in 3 patients with GLUT1 transporter deficiency syndrome (GLUT1-DS), also known as De Vivo disease. The CSF metabolome also showed very low levels of glucose, fructose, and mannose and very high levels of glutamine and inosine suggestive of GLUT1-DS.

The Condition

GLUT1-DS is a rare autosomal dominant disorder due to a mutation in or deletion of the *SLC2A1* gene found at chromosomal location 1p34.2, which encodes for GLUT1 transporter that is responsible for basal glucose across the blood-brain barrier. Symptoms result from neuroglycopenia due to inability of glucose to be transported from the blood to the brain. The classic presentation includes early-onset seizures and neurodevelopmental delays in infancy or childhood. Some patients present with a nonepileptic form with paroxysmal movement disorders in childhood or even later in adulthood with intermittent ataxia, choreoathetosis, dystonia, or alternating hemiplegia. Rarely, the condition is inherited in an autosomal recessive manner. Hypoglycorrhachia (low CSF glucose level) with a normal serum glucose level (measured simultaneously) is the accepted standard for making this diagnosis. Ideally, CSF and serum glucose levels should be measured after 4 hours of fasting. The level of CSF glucose is typically less than 60 mg/dL (<3.3 mmol/L) (in most cases it is <40 mg/dL [<2.2 mmol/L]). The CSF/blood glucose ratio is usually less than 0.4. Other abnormal biochemical tests include low or low normal CSF lactate. An uptake assay to measure glucose transport across the cell membrane can be performed by assessing erythrocyte 3-O-methyl-D-glucose uptake. It is expected to be abnormally low, but this test may not be readily available. Molecular genetic testing can confirm the diagnosis by detecting a pathogenic variant in the *SLC2A1* gene by sequence analysis or deletion/duplication analysis. Metabolome testing is a newly emerging study that can assess hundreds of small metabolites with a single screening test looking at perturbations in biochemical pathways. It can aid in the diagnosis of many inborn errors of metabolism. In GLUT1-DS, CSF metabolome analysis is expected to show low levels of glucose, fructose, and mannose along with high levels of glutamine and inosine.

Treatment

Antiepileptic drugs are ineffective in treating GLUT1-DS. The treatment of choice is the ketogenic diet because ketones cross the blood-brain barrier through MCT1 transporter not GLUT1 transporter. Ketones provide an alternative source of energy to brain cells. Studies have shown that early identification of this disease and early management with the ketogenic diet are associated with better neurodevelopmental outcomes. Our patient became seizure-free and his electroencephalogram normalized after the ketogenic diet was initiated. He was not taking any antiepileptic drugs on discharge. At the follow-up visit at 4 months of age he showed age-appropriate growth and development and remained seizure-free solely on the ketogenic diet. It is possible that our patient's family history of seizures in the mother, maternal aunt, and her son is due to GLUT1-DS, but the family refused further genetic testing.

Lessons for the Clinician

- Subtle seizures should be included in the differential diagnosis of apnea in newborns.
- Clinicians should be aware that although low cerebrospinal fluid glucose (hypoglycorrhachia) can be suggestive of an infectious etiology, it is not always the case. Other causes of hypoglycorrhachia, such as GLUT1 transporter deficiency syndrome (GLUT1-DS), should be considered, particularly if the patient has a concomitant seizure or movement disorder.
- Clinicians should be aware of the broad spectrum of presentation of GLUT1-DS from infancy into adulthood and the importance of early recognition of this disorder. The ketogenic diet should be started promptly on suspicion of this disorder because it is the only proven effective treatment to improve neurodevelopmental outcomes.

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Mastoiditis

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AUTHOR DISCLOSURE Dr Kynion has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Acute mastoiditis (AM) is an uncommon but potentially serious sequelae of acute otitis media (AOM). In the preantibiotic era it complicated up to 20% of cases of AOM. Currently, the incidence of AM has fallen to 1.2 to 4.2 cases per 100,000 children per year. The peak age of incidence of AM is in the first 1 to 2 years of life.

Mastoid air cells have a direct physical connection to the middle ear space through the aditus ad antrum. Inflammation of the middle ear typically affects the mastoid mucosa in a similar manner. In this way, virtually all cases of AOM are associated with some degree of mastoid inflammation.

If this initial mastoid inflammation results in blockage of the aditus ad antrum, pus and edema may accumulate, leading to periostitis. If the destruction affects the delicate trabecular system it will create a type of empyema called a coalescent mastoiditis. If the infection breaks through the mastoid cortex but becomes trapped by the periosteum it will result in a subperiosteal abscess. Most worrisome is when the infection extends beyond the mastoid itself. There are multiple anatomical structures that are at risk and can lead to intracranial complications: sigmoid sinus (thrombosis), occipital bone (osteomyelitis), subdural/epidural spaces (abscess), meninges (meningitis), attached musculature (Bezold abscess), facial nerve (paralysis), and labyrinth (suppurative labyrinthitis).

On physical examination there is evidence of otitis media on otoscopy. Over the mastoid itself, one will classically see evidence of tenderness, erythema, edema, or fluctuance. In many cases, the mastoid swelling will cause the auricle to protrude anteriorly and inferiorly. Of note, these classic signs are not seen in all cases of confirmed AM. In addition, these signs are less common in patients who are already taking antibiotics, so clinicians should maintain an index of suspicion in all cases of AOM.

Acute mastoiditis is defined as having these signs and symptoms less than 1 month in total duration. In contrast, cases of chronic mastoiditis exceed 1 month and typically consist of chronic ear drainage and conductive hearing loss. A third classification is subacute or "masked" mastoiditis, which may be precipitated by inadequate antibiotic treatment of AOM. This may lead to a low-grade persistent infection manifested by a chronic middle ear effusion or recurrent AOM. Subacute mastoiditis is associated with a greater incidence of intracranial complications, such as meningitis, lateral sinus thrombosis, and brain abscess.

Although there are reports of successful treatment of AM without the attempted recovery of the organism, most experts recommend, at a minimum, performing a tympanocentesis to obtain material for culture and sensitivities. Many institutions opt to place a tympanostomy tube to promote continued drainage, relieve pain and pressure, and possibly obviate the need for further surgical intervention. This recommendation is especially strong for patients younger than 2 years.

Routine laboratory tests do have a limited role in the evaluation of AM. Both an elevated white blood cell count and C-reactive protein (CRP) level are associated

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with an increased need for surgical intervention. Patients with a CRP level greater than 72 mg/L (686 nmol/L) tend to have more intracranial complications. Also, obtaining serial CRP levels may be helpful in determining whether a patient is responding appropriately to therapy. Blood cultures may be obtained but have only a 3% to 6% recovery rate.

The microbiology of AM tends to mirror that of AOM. *Streptococcus pneumoniae* is the most common organism isolated. Other notable pathogens include *Streptococcus pyogenes, Staphylococcus aureus* (methicillin sensitive and resistant), *Haemophilus influenzae,* and *Fusobacterium necrophorum.* The introduction of pneumococcal conjugate vaccine (PCV) 7 (July 2009) and PCV13 (November 2010) have resulted in a modest reduction in AM overall with a shift toward serotypes not covered by the vaccines. Of note, after PCV7 was introduced there was a significant increase in recovery of serotype 19a. Serotype 19a is included in PCV13, but the reported efficacy of PCV13 in preventing infections with serotype 19a is mixed. Some studies show a clear decrease in its incidence, but others show the incidence of serotype 19a to have remained stable or even increased. This serotype is of particular interest because a significant number are multidrug resistant and are associated with more invasive complications, such as a subperiosteal abscess.

In chronic mastoiditis, the recovered organisms tend to be polymicrobial and include *Pseudomonas aeruginosa,* Enterobacteriaceae, *S aureus,* and anaerobes such as *Peptostreptococcus,* gram-negative bacilli (*Prevotella, Porphyromonas,* and *Bacteroides*), and *Fusobacterium.* Rarely, *Mycobacterium tuberculosis,* nontuberculous mycobacterium, and *Mycobacterium bovis* are isolated.

Empirical parenteral antibiotic treatment must consider the known microbiology of mastoiditis and local antibiotic resistance patterns. Past studies have supported the empirical use of ceftriaxone or cefuroxime often combined with clindamycin for anaerobic coverage. Some experts, citing widespread antibiotic resistance, recommend vancomycin as initial monotherapy as long as the child does not have a history of recurrent AOM or antibiotic use in the preceding 6 months. For patients with this history of recurrent AOM or recent antibiotic use, they recommend using vancomycin with ceftazidime, cefipime, or piperacillin-tazobactam to add coverage for *P aeruginosa.* If cultures are obtained and are positive, then clinicians may modify the antibiotic(s) based on sensitivities and the patient's clinical condition.

Overall there has been a shift away from surgical intervention and toward medical management. One algorithm is proposed by Chesney: start patients with AM on intravenous (IV) antibiotics with or without myringotomy or pressure equilization tube placement. If these patients worsen or do not improve after 48 hours of IV antibiotics, then proceed with a temporal bone computed tomographic (CT) scan with contrast. If the CT scan is positive for intracranial complications, then perform a mastoidectomy. Most patients (60%–87%) improved without surgery or CT scanning, making it a viable option for uncomplicated cases of AM.

This more selective use of temporal bone CT scanning illustrates the delicate balance of limiting exposure to ionizing radiation versus the need to detect serious complications. A CT scan is reported to be 90% to 100% sensitive but only approximately 40% specific. It is indicated, however, if there are neurologic signs of central nervous system infection, evidence of intracranial complications, development of a cholesteatoma, deterioration in clinical status, or failure to improve after 48 hours of IV antibiotic therapy. If results of the CT scan are abnormal, the recommendation is to proceed with mastoidectomy.

Another notable trend is in the treatment of a subperiosteal abscess. Previously, all such cases underwent mastoidectomy, but this procedure is associated with the development of cholesteatomas, recurrent middle ear infections, and/or hearing loss. Some surgeons have advocated posterior auricular aspiration, but this option is limited somewhat by the risk of the abscess reaccumulating. A third option is performing incision and drainage of the abscess under local anesthesia. This procedure has a 92% success rate and may be considered an initial option for many of these cases.

In summary, mastoiditis is an uncommon but potentially serious complication of a common disease. Despite the widespread use of antibiotics, it is a disease that merits consideration in every case of suspected AOM and that may not present in the classic manner. Mastoiditis research is ongoing but is hampered by inconsistent diagnostic criteria, shifting microbiology, and wide practice variance in medical versus surgical management options.

Note. The views expressed in this manuscript are those of the author and do not reflect the official policy or position of the Department of the Army, Department of Defense, or US Government.

COMMENT: Dr Kynion's *In Brief* reminds me of how medical care has changed for mastoiditis during the past 3 decades and the importance of continued evaluation of how we care for patients through research. Although mastoiditis has fortunately become a less common complication of AOM, the development of mastoiditis must still be considered, even in children as young as 4 months of age, and younger infants may progress to more serious disease more quickly. I have been involved with several cases where a pediatric patient had a brain CT scan performed for a different etiology and mastoiditis was suggested based on fluid in the mastoid, but no other symptoms were present. This is an example where the correct diagnosis depends on a complete physical examination with finding the presence of AOM in addition to findings of tenderness, erythema, or edema over the mastoid area and in classic cases protrusion of the auricle. This *In Brief* also demonstrates the importance of studies promoting high-value, cost-conscious care. More selective use of CT scanning (for patients with signs of intracranial pathology or lack of improvement with IV antibiotic therapy) and mastoidectomy may contribute to less morbidity, higher quality of care, and lower medical costs for patients and their families.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

in Brief

Brain Abscess

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AUTHOR DISCLOSURE Dr Weinberg has disclosed that he was principal site investigator on a research grant awarded to the University of Rochester for a Merck-sponsored clinical trial of caspofungin in NICU patients with yeast infection and that he has written and edited chapters for the *Merck Manual of Diagnosis and Therapeutics* book and website. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Abscesses are focal infections consisting of encapsulated pus and pyogenic bacteria, or, less commonly, mycobacteria, fungi, or protozoa. Abscesses of the central nervous system may be found in the brain parenchyma itself, as well as in the intracranial epidural space and spinal epidural space. Although rare in children, brain abscesses must be recognized promptly to prevent significant morbidity and mortality.

The annual incidence of bacterial brain abscesses in the general population is as high as 0.3 to 1.3 per 100,000 population; recent case series of pediatric brain abscesses have estimated the annual incidence to be approximately 0.5 per 100,000 children. The rarity of brain abscesses precludes accurate determination of whether the annual incidence is decreasing (as might be expected given the availability during the past 70 years of antibiotics for infections predisposing to brain abscess and the development of corrective surgery for many congenital heart defects) or increasing (as might be expected with advances in sophisticated diagnostic cranial imaging such as magnetic resonance imaging [MRI]).

Predisposing factors are found in most (~80%) of cases of brain abscess; approximately 20% of abscesses in modern case series are idiopathic. Among cases with predisposing factors, 30% to 50% stem from a contiguous focus of infection (eg, otitis media, mastoiditis, sinusitis, or orbital cellulitis); approximately 30% are associated with bacteremia (eg, cyanotic congenital heart disease, pulmonary disease, or odontogenic infection); approximately 10% result from disruption of the body's natural barriers (eg, neurosurgical procedure or head trauma); and approximately 10% occur in the presence of an immunosuppressive condition (eg, solid organ transplant or leukemia).

Brain abscesses associated with a contiguous focus of infection are often caused by *Streptococcus* species, including *Streptococcus pneumoniae* and *Streptococcus anginosus,* as well as anaerobic and microaerophilic bacteria (eg, *Bacteroides fragilis, Eikenella corrodens, and Abiotrophia* and *Granulicatella* species). In contrast, the most common causative organisms in patients with head trauma or neurosurgical procedures are *Staphylococcus aureus,* coagulase-negative staphylococci, or gram-negative bacilli. Very rarely, organisms such as *Actinomyces* species, *Nocardia* species, *Mycobacterium tuberculosis, Candida* species, *Aspergillus* species, or *Toxoplasma gondii* may cause brain abscesses, especially in immunocompromised children. At least 25% of brain abscesses yield polymicrobial growth in culture, an important consideration in treatment decisions.

Somewhat surprisingly, bacterial meningitis in children and adults is very rarely associated with brain abscess, despite the intense inflammation and bacterial load in the meninges covering the brain. However, neonates with unusual gram-negative meningitis, caused by *Citrobacter* species or *Cronobacter* (formerly *Enterobacter*) *sakazakii,* very frequently (85%) develop 1 or more brain

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abscesses. The virulence factors of these 2 groups of unusual pathogens that lead to brain abscess formation are not well-understood.

When the brain parenchyma is infected, the first manifestation is a focal cerebritis with surrounding edema, which is then encapsulated over days to weeks by inflammatory granulation tissue surrounding the core of necrotic tissue. Where in the brain an abscess develops generally depends on the source of infection: sinusitis, especially frontal, and infections of the oral cavity tend to cause frontal lobe abscesses, and otitis media and mastoiditis lead to abscesses in the parietal/temporal region.

Fever is present in 50% of patients with a brain abscess, and a history of headaches is even more common, in 60% to 70%. Although older patients may localize their headaches toward the site of the abscess (right or left side, front or back of the head), young children usually cannot. Approximately half of all patients have focal neurologic findings, and approximately 25% have seizures.

The classic clinical triad suggestive of brain abscess—fever, headache, and focal neurologic findings—is more specific than sensitive, as only 20% of affected patients exhibit all 3 at diagnosis. If the abscess has been present for long enough or is big enough to significantly increase intracranial pressure, papilledema may be found on examination; this is in contrast to bacterial meningitis, which presents too quickly for papilledema to develop.

Whereas the child with possible or probable acute bacterial meningitis requires prompt lumbar puncture for diagnosis, the most important initial study for diagnosis of brain abscess is cranial imaging, with either MRI or computed tomographic (CT) scanning with intravenous (IV) contrast. A hypodense lesion on CT scanning is consistent with the cerebritis of a newly forming abscess, and focal edema on MRI suggests the presence of a mass lesion. As an abscess matures, IV contrast yields a classic ring-enhancing image with a necrotic center and surrounding edema. Diffusion-weighted MRI can distinguish brain abscesses from other cerebral masses with diagnostic sensitivity and specificity greater than 95% by showing a homogenous, hyperintense signal with corresponding hypointense signal on the apparent diffusion coefficient sequence.

Again, unlike the situation with suspected meningitis, a lumbar puncture should not be performed when brain abscess is a serious consideration because of the risk of herniation from elevated intracranial pressure and because CSF is not likely to identify the infecting pathogen. In a meta-analysis of patients with brain abscess who did have a lumbar puncture because of uncertainty of diagnosis, only 25% had a positive CSF culture, but 7% had clinical deterioration attributed to the procedure. Identification of the causative organism is best attempted by obtaining Gram-stain and culture information on material obtained through stereotactic aspiration of the abscess. Blood cultures may identify the causative organism in one-third of cases. If culture is negative but bacterial abscess is strongly suspected, performing a polymerase chain reaction amplification of bacterial 16S ribosomal DNA sequences may be able to detect bacterial DNA; however, such testing is not yet standardized or routinely available.

Management of brain abscess may require multidisciplinary input of critical care, neurosurgical, neurologic, and infectious diseases experts. Associated lesions may require consultants in otorhinolaryngology and ophthalmology as well.

Neurosurgical intervention is generally undertaken in most patients with brain abscesses, both for etiologic diagnosis and reduction of lesion size. Stereotactic aspiration via a burr hole is now the most common procedure, rather than craniotomy. Excision of the entire abscess itself is performed in approximately 25% of patients, especially in those with abscesses larger than 2.5 cm or in cases of symptomatic cerebral edema or ventricular rupture. In stable patients with multiple abscesses, none of which are greater than 2.5 cm in diameter, nonsurgical management with antibiotic therapy has had success in some reports.

Intravenous antimicrobial therapy should be given without delay to patients with a brain abscess; antibiotic therapy should be deferred only if aspiration or surgery can be accomplished in the next few hours. The empirical choice of agent(s) should depend on the most likely organism(s). Thus, for cases likely to have spread from the middle ear, sinuses, or orbits, a third-generation cephalosporin (cefotaxime or ceftriaxone) plus metronidazole is appropriate (with the addition of vancomycin if methicillin-resistant *S aureus* is suspected). An alternative regimen suggested by some experts is meropenem with or without metronidazole. If head trauma or a neurosurgical procedure is thought to be a factor, vancomycin plus metronidazole, plus a third- or fourth-generation (cefepime) cephalosporin is indicated. In children who are immunosuppressed, therapy may need to be directed against *Nocardia* (trimethoprim-sulfamethoxazole), *Aspergillus* or other fungi (voriconazole), or *Toxoplasma* (pyrimethamine-sulfadiazine).

The duration of IV antibiotic therapy is typically 6 to 8 weeks, sometimes followed by a course of an oral agent such as amoxicillin–clavulanic acid or metronidazole. Some experts have advocated for shorter IV courses (eg, 2 weeks) followed by oral therapy for several weeks to months. The success of therapy should be monitored with serial CT scans or MRIs; imaging should confirm significant improvement at the end of planned therapy. Corticosteroids are sometimes used to reduce brain edema in symptomatic patients, but at the risk of reducing antimicrobial penetration. Some, but not all, experts administer anticonvulsants for several months.

The main complications of brain abscess are hydrocephalus from direct compression by a posterior fossa abscess and ventriculitis from rupture of an abscess into the ventricular system, which carries a 27% to 85% mortality rate. Other complications include increased intracranial pressure, brain herniation, and status epilepticus. The case fatality rate of brain abscess has declined substantially in the past 6 decades with improvements in cranial imaging, neurosurgical techniques, and antimicrobial therapy. Since 2000, mortality has been 5% to 10%, compared with 40% in the 1960s, and 70% of patients have a good outcome with minimal or no neurologic sequelae.

COMMENT: Interesting. Are we seeing more brain abscesses these days because our diagnostic tools, particularly MRI, have become so much more precise; or have our more effective modalities for treating and even preventing the conditions that predispose to brain abscess (add pneumococcal vaccines to the antibiotics and corrective heart surgeries mentioned by Dr Weinberg) significantly reduced its real incidence? That's an unanswered question we should be pleased to live with, not much of a price to pay for the incredible progress medicine has made. Any of us old enough to have seen a patient tortured by undergoing a pneumoencephalogram (you youngsters can look it up) has to be overcome with gratitude for what our modern imaging techniques offer. And other than sewers, antibiotics and vaccines have been the greatest boons to public health that human ingenuity has yet devised.

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR MAY 2018 PEDIATRICS IN REVIEW

Pediatric Vision Screening: 1. C; 2. E; 3. E; 4. B; 5. B.
Screening for Poverty and Poverty-Related Social Determinants of Health: 1. E; 2. A; 3. B; 4. C; 5. B.
Bordetella pertussis (Pertussis): 1. D; 2. C; 3. D; 4. B; 5. C.

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Visual Diagnosis

Visual Impairment, Polydactyly, and Obesity: Red Flags in a Child

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PRESENTATION

A 6-year-old boy who recently emigrated from Afghanistan presents for a routine health supervision visit. His parents are concerned about his progressive poor night vision, and he has polydactyly in the right hand. Speech and motor development are delayed. He started walking and talking late, at approximately 2 years of age according to his parents.

He was born at full term via normal vaginal delivery and had an unremarkable hospital course. He had extra digits on the bilateral upper and lower extremities consisting of 6 and 7 digits, respectively. All the extra digits were surgically removed at 1 year of age, except the sixth digit in the right hand (Fig 1A), which was left on the parents' request. There are healed surgical scars secondary to the removal of extra digits from the left upper extremity and both lower extremities (Fig 1B). He has short stature (height for age is at the third percentile) and truncal obesity (body mass index >95th percentile) (Fig 2).

The father and mother are first cousins. Of the other 3 siblings, a 5-year-old brother has similar findings, including polydactyly, short stature, obesity, and hearing impairment. Other family members are healthy.

The patient is evaluated by an optometrist and is noted to have abnormal findings on eye examination (Fig 3), which prompts referral to a retinal specialist.

DIAGNOSIS

Based on the constellation of clinical features and examination findings, our patient has Bardet-Biedl syndrome (BBS). He met 4 of 6 primary clinical features (retinitis pigmentosa, polydactyly, truncal obesity, and learning difficulties). The differential

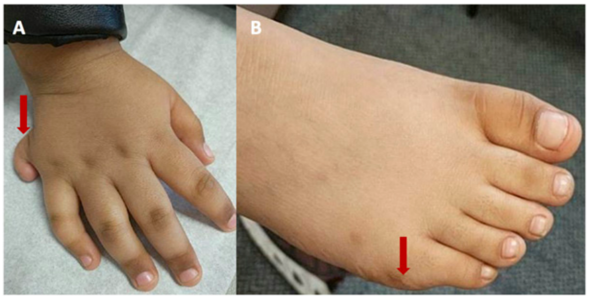

Figure 1. Polydactyly of the right upper extremity (A) and a surgical scar from removal of an extra digit from the right lower extremity (B).

AUTHOR DISCLOSURE Drs Agrawal, Dokania, and Allen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

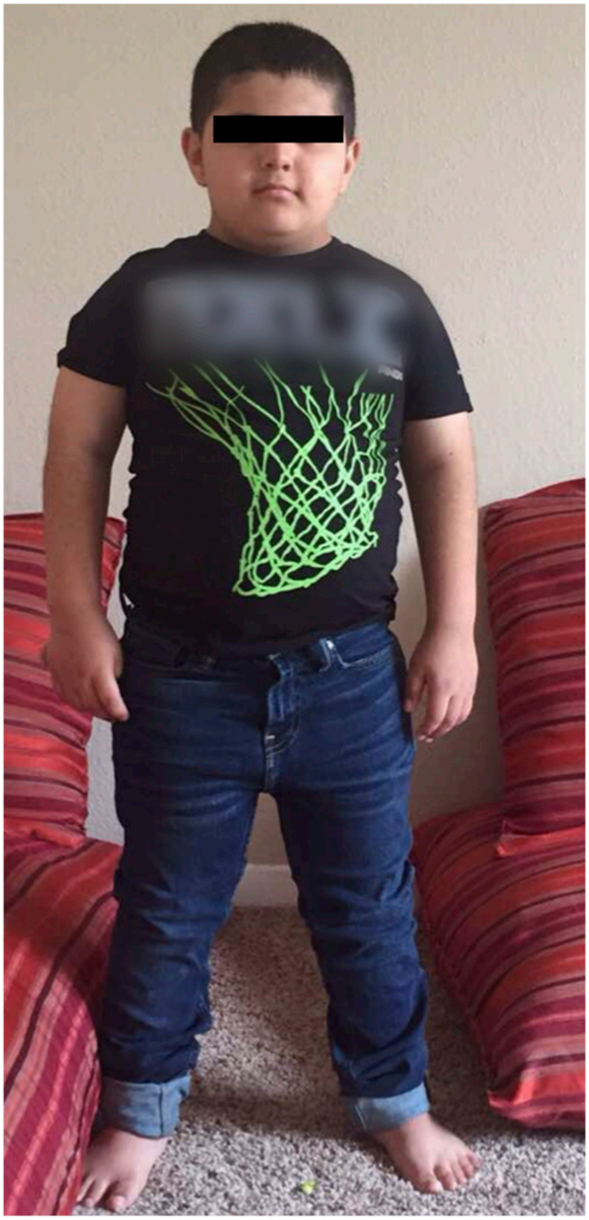

Figure 2. Patient photograph showing truncal obesity and short stature.

diagnosis of BBS includes Laurence-Moon syndrome, Alstrom syndrome, Joubert syndrome, Meckel syndrome, McKusick-Kaufman syndrome, Prader-Willi syndrome, Biemond syndrome type II, or Senior-Loken syndrome.

DISCUSSION

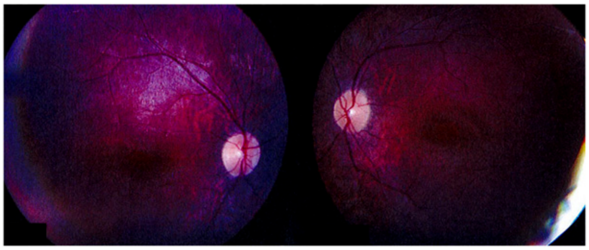

Figure 3. Fundoscopic image showing bilateral pigmentary retinopathy around the optic nerve.

Originally described in 1866, (1) BBS is a rare genetic disorder typically inherited as an autosomal recessive disease. However, digenic and trigenic inheritance has been described. So far, at least 20 genes have been identified, all of which interfere with primary ciliary function, leading to multisystem organ involvement. (2) Hence, BBS is referred to as ciliopathic disorder. There is significant heterogeneity in the genetic defects, leading to a wide spectrum of clinical manifestations. Clinical presentation varies with respect to age at onset and severity of presentation/progression in affected individuals even within the same family. The diagnosis is primarily based on clinical criteria. Other than polydactyly, symptoms/signs are usually not present at birth but appear in the first and second decades of life. Commonly the clinical features are seen during 6 to 8 years and progress during the second decade. Symptoms are classified into primary and secondary manifestations. Primary clinical features include rod-cone dystrophy (93%), polydactyly (63%–81%), truncal obesity (72%–92%), genital anomalies (59%–98%), renal abnormalities (53%), and learning difficulties (61%). (3)(4) Secondary features include developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia/poor coordination, olfactory deficit, and congenital heart disease. (3)(4) Diagnosis is confirmed with the presence of 4 of 6 primary features or 3 primary and 2 secondary features. (3)(4)

The most debilitating and common complications are ocular, resulting from rod-cone dystrophy usually in the first decade of life initially affecting night and peripheral vision due to degeneration of rod photoreceptors. Most patients become legally blind by the second or third decades of life. (5) Renal diseases, including cystic tubular disease, lower urinary malformation, chronic glomerulonephritis, and defective tubular concentrating abilities, are the major causes of morbidity and mortality in these patients. Abnormal renal function leading to end-stage renal disease is present in 53% to 82% of affected individuals. Such patients have anemia, polyuria and polydipsia in later childhood. (3)(4) Cardiac abnormalities include aortic stenosis, patent ductus arteriosus, and cardiomyopathy. (3)

MANAGEMENT

Given the autosomal recessive mode of inheritance, risk of recurrence is 25% in siblings of affected patients. Hence, genetic diagnosis and counseling plays a crucial role in planning future pregnancies. Management is mainly symptomatic. Multidisciplinary involvement and close monitoring are necessary. Suspected patients should be evaluated by various specialties, including genetics, endocrinology, cardiology, speech therapy, audiology, nephrology, and ophthalmology. Screening of affected family members is also necessary. Baseline monitoring of renal/liver/thyroid function tests, glucose/lipids/sex hormones, renal ultrasonography, blood pressure, hearing, and detailed eye examination are necessary. Annual clinical follow-up with periodic reevaluation of all organ systems is necessary.

PATIENT COURSE

The family underwent genetic counseling. Genetic testing with whole exome sequencing is pending. Renal ultrasonography showed thinning of the renal cortex and increased echogenicity of renal pyramids bilaterally. The patient has a structurally normal heart. He has been prescribed eyeglasses. He has normal hearing sensitivity in each ear. He has normal renal/thyroid/liver function test results and normal glycemic control. He is following a healthy diet and lifestyle. He is enrolled in special classes at school and is receiving weekly speech therapy.

Summary

- Bardet-Biedl syndrome (BBS) is generally inherited in an autosomal recessive pattern.
- A constellation of visual impairment, truncal obesity, polydactyly, and learning difficulty should raise suspicion for BBS.
- The clinical presentation is heterogeneous, with variable onset and progression to multiorgan involvement.
- Diagnosis is based on the presence of either 4 of 6 primary features or 3 primary and 2 secondary features.
- Genetic diagnosis and counseling is crucial for affected family members.
- Management of BBS is symptomatic, and patients require periodic follow-up with a multidisciplinary team.

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Suggested Readings

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Visual Diagnosis

Newborn Girl with Congenital Unilateral Eye Opacity

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PRESENTATION

A newborn infant girl born small for gestational age (SGA) at 39 weeks via spontaneous vaginal delivery to a 17-year-old gravida 1 para 1 woman from El Salvador who has no significant medical history presents with a unilateral right eye opacity. The mother's pregnancy was complicated by hyperemesis in the first trimester, urinary tract infection during the second trimester, and poor weight gain (only 1.8 kg). The mother reports no sexually transmitted infections or other previous infections. The mother does report a history of marijuana use before this pregnancy but no other drug, tobacco, or alcohol use. The mother also has no history of recent travel or contact with anyone who has traveled outside the United States. No structural or anatomical abnormalities were detected on prenatal ultrasonography at 11, 18, 21, 34, and 37 weeks' gestation.

The baby had Apgar scores of 8 at 1 minute and 9 at 5 minutes, normal resuscitation, and maternal laboratory screenings that were negative for infections. The patient is noted to have a right corneal opacity and small growth parameters based on the World Health Organization growth standards for girls aged 0 to 2 years (microcephaly with fronto-occipital circumference at the sixth

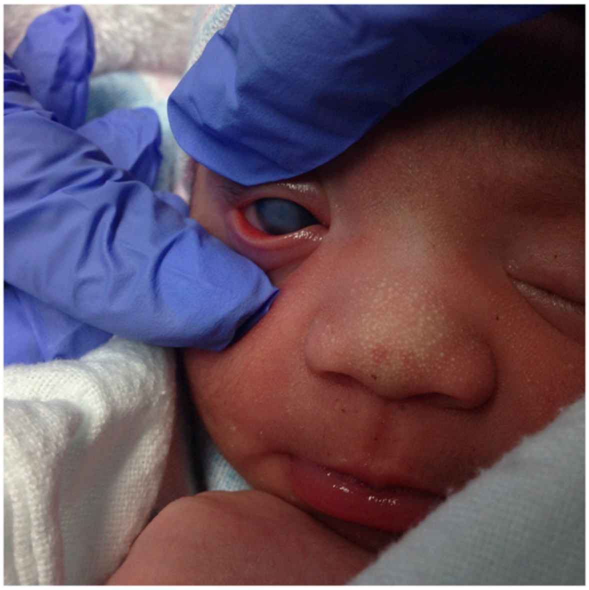

Figure 1. Frontal view of right eye opacity.

AUTHOR DISCLOSURE Mr Wang and Drs Kubota and Bayona have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

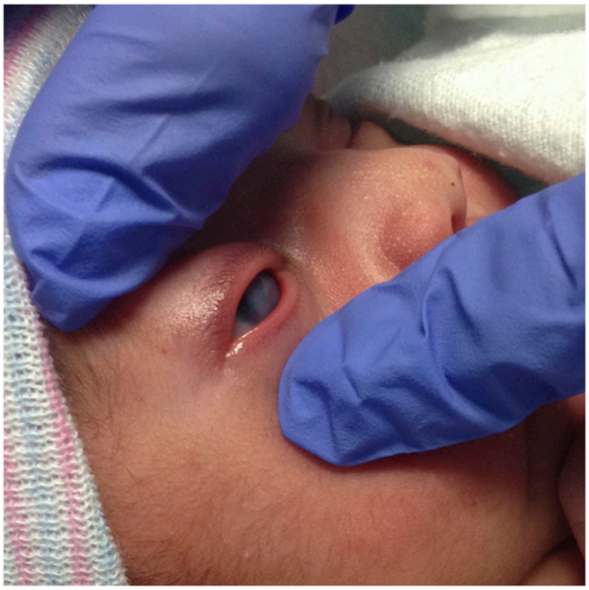

Figure 2. Lateral view of right eye opacity.

percentile and SGA with length at the 36th percentile and weight at the fifth percentile). On physical examination, the patient is small and alert, with normal facies and normally set ears. The patient's skin is pink, warm, and without rashes. She appears microcephalic, with the anterior fontanelle open soft and flat, nares patent, and palate intact. She has strong suck and grasp reflexes and no lymphadenopathy. Cardiovascular, pulmonary, and abdominal examination results are normal. The patient has normal female genitalia; there were no limb deformities, with no sandal toe or single palmar crease; and all the extremities moved symmetrically and spontaneously.

Ocular physical examination reveals a clear left eye with no discharge and a cloudy right eye without discharge or tearing (Fig 1). Red reflex is elicited on the left eye only. Full extraocular motility is apparent in both eyes. Intraocular pressure and corneal diameter are normal in both eyes. The right eye lens is not visible, and the right iris is pulled up toward the cornea superiorly (Fig 2). A clinical diagnosis is made.

DIAGNOSIS

The presence of corneal opacification, normal intraocular pressure, normal corneal diameter, and incomplete separation of the cornea and iris suggest the diagnosis of unilateral Peters anomaly.

DISCUSSION

Peters anomaly is a rare condition of anterior segment dysgenesis causing a cloudy appearance of the cornea. Vision is typically blurred or decreased, and patients can become legally blind. Size and intensity of the opacification can vary from a streak to encompassing the entire front surface of the cornea. Peters anomaly is described as type I or type II, with both forms exhibiting cornea opacification and tending to be bilateral in 80% of cases. (1)(2) Type I has a cloudy central cornea with attachments from the cornea to the iris. Type II has the same cornea opacity with the addition of a cataract and/or attachments from the cornea to the lens. (3)

Most cases of Peters anomaly are sporadic and isolated but can be inherited involving mutation of the *PAX6*, *FOXC1*, *PITX2*, or *CYP1B1* genes, which are involved in the development of the anterior segment of the eye. (4)(5) The condition manifests in utero during the first trimester when neural crest migration is disrupted in the development of the anterior segment of the eye. Peters anomaly is commonly associated with other ocular or systemic abnormalities. Ocular abnormalities include amblyopia, strabismus, glaucoma, cataracts, microphthalmia, sclerocornea, iris hypoplasia, aniridia, and coloboma. (6) Systemic abnormalities include trisomies, partial chromosomal deletions, 49XXXXY syndrome, Axenfeld-Rieger syndrome, Krause-Kivlin syndrome, Norrie disease, Cri-du-chat syndrome, and Peters plus syndrome. (4)(5) Thus, it is important to evaluate patients for dysmorphic facial and limb features, short stature, developmental delay, neurologic impairments, cardiac anomalies, and genitourinary abnormalities.

Diagnosis is made clinically by ocular anterior segment examination. Additional tests include B-scan ultrasonography, ultrasonographic biomicroscopy, and genetic testing. Treatment may not be necessary in all cases, but surgical corneal transplant with penetrating keratoplasty and iridoplasty should be considered. (7) The success rate of keratoplasty in Peters anomaly type I is 87.5% versus 14.2% in type II. (1) Aside from ophthalmology consultation for cornea opacification, Peters anomaly can also have other systemic problems, as noted previously herein, and may require evaluation by cardiology, urology, and neurosurgery specialists.

Infants with Peters anomaly have a 50% to 70% risk of associated congenital glaucoma due to related angle anomalies of the anterior segment of the eye. (2) The eyes commonly present with cataracts and the lens attached to the posterior cornea. The increase in intraocular pressure may develop over time and lead to potential irreversible vision loss, which is why close monitoring is required. Surgical intervention may be necessary if glaucoma develops, with long-term visual outcome dependent on corneal status and the presence of any concurrent eye diseases. (2)(8) Major postoperative complications include retinal detachment, phthisis, graft failure, and cataract.

Genetic evaluation with gene sequencing for *PITX2, PAX6, FOXC1,* or *CYP1B1* and additional testing such as karyotype or whole exome sequencing may help in detecting possible associated syndromic conditions. Unlike bilateral Peters anomaly cases, which have been associated with a higher rate of syndromic malformations, unilateral Peters anomaly is usually not syndromic and does not typically require further genetic testing. (1) However, when unilateral cases are coupled with the additional presentation of growth or development defects, then genetic evaluation may be necessary. Most of Peters anomaly cases do not have a genetic diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosisfor congenital corneal opacification includes Peters anomaly, congenital glaucoma, congenital keratitis, congenital corneal dystrophy, sclerocornea, corneal dermoid, metabolic disorders (mucopolysaccharidosis), and birth trauma. Glaucoma was unlikely due to the normal intraocular pressure and corneal diameter. Keratitis was unlikely as the maternal laboratory screenings were negative for infections. Corneal dystrophy was unlikely as the patient's ocular defect presented as unilateral and there was no family history of ocular defects. Anterior segment visual inspection was not consistent with sclerocornea or corneal dermoid. The patient was negative for distinctive identifiable disorder or syndromic features. Birth trauma was also unlikely due to the patient being born via uncomplicated spontaneous vaginal delivery without the use of forceps.

PATIENT COURSE

The patient was admitted to the well-baby nursery. Ophthalmology was consulted and diagnosed Peters anomaly. The patient received routine newborn care and had no syndromic features or abnormalities on examination. The patient underwent glucose monitoring for the first 24 hours after birth every 3 hours due to SGA and was normoglycemic. A Zika screen was considered due to microcephaly, ocular impairment, and the mother having recently come from El Salvador; however, the mother did not exhibit any signs of infection during pregnancy and denied any travel during pregnancy or having any travel contacts, so a Zika screen was not warranted. Head ultrasonography to evaluate microcephaly revealed no structural abnormalities. The patient was discharged after 2 days. Regular pediatric and ophthalmology follow-ups were recommended to assess a plan for Peters anomaly, screen for the development of glaucoma, and monitor for developmental problems.

The patient was seen at 3 months of age by a pediatric genetic counselor for genetic screening. At this time, the patient's ocular findings were unchanged and the patient's growth parameters had normalized: weight, 6.45 kg (75th–90th percentile); length, 62.5 cm (90th–95th percentile); and fronto-occipital circumference, 38 cm (25th–50th percentile). Because the patient was not having trouble gaining weight after birth and was developing appropriately, there was low suspicion for a genetic abnormality associated with SGA status at birth. Thus, chromosomal analysis and molecular genetic testing were not recommended at that time, and the patient was to follow up in 1 year.

Summary

- Peters anomaly is a clinical diagnosis that is typically bilateral but may be unilateral.
- Peters anomaly should prompt further investigation for associated ocular abnormalities and potential systemic malformations, and close regular monitoring is needed to prevent further complications.
- Infants with Peters anomaly are at increased risk for glaucoma due to related angle anomalies of the anterior segment of the eye.
- Genetic testing for underlying syndromic conditions may be warranted if growth defects or developmental delays are present.

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Burn Care for Children

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Education Gap

Burn injuries are common in children. Management of these injuries and their consequences will be part of most busy general pediatric practices. Although most burns in children are small and can be managed with care provided in the outpatient setting, there is a significant number of children with more serious burn injuries whose acute and long-term management will involve a collaboration between the regional burn program and the child’s pediatrician. An understanding of the practice of outpatient small burn care is important. Also useful is a grasp of the concepts of inpatient burn care and long-term burn aftercare.

Objectives After completing this article, readers should be able to:

1. Understand the local and systemic physiologic changes caused by burns so that they can best understand therapeutic options.
2. Describe the essential components of outpatient care of small burns.
3. Grasp the essential components of inpatient care of more serious burns.
4. Develop an awareness that long-term physical and emotional outcomes can be enhanced through participation in burn aftercare programs that include scar management, burn-specific physical and occupational therapy, ready access to burn reconstruction, emotional counseling, and family and peer support.
5. Have an awareness of the nonburn conditions commonly treated in burn units.

AUTHOR DISCLOSURE Dr Sheridan has disclosed that he has a research grant for burn outcomes from Shriners Hospital for Children and a grant for clinical research for burn depth determination from Physical Sciences Inc/the Department of Defense and that he is a consultant for developing burn mapping software for SimQuest. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

INTRODUCTION

The first objective of this review is to familiarize the reader with the local and systemic changes caused by burns and relate these to the immediate and long-term practical needs of children who have experienced such injuries. The second objective is to familiarize the reader with how burn care is organized and how general pediatric practices and hospitals can collaborate with regional burn programs to provide quality care of burns and burnlike conditions for children.

Epidemiology and Etiology

Burns are common injuries caused by a variety of etiologic mechanisms. Both incidence and mechanism vary with age and socioeconomic status. In developed countries, infants and toddlers are particularly vulnerable, most commonly injured by scalding in bath and kitchen incidents (Fig 1). In low-income countries, incidence and severity tend to be higher because of fewer mandated electrical safety precautions and more primitive living and cooking conditions. (1)(2) Around open fires, young children are particularly at risk for accidental burn injury.

Prevention

Efforts to reduce burn incidence have had mixed success. (3) Product safety regulations have included flame-retardant sleepwear, fire-safe cigarettes, hot water heater temperature set caps, and mandatory hard-wired smoke detectors. A large number and variety of public education programs have also been championed. Despite these legislative efforts, much work remains to be done to craft a broadly effective burn prevention strategy. Individual family counseling in conjunction with well-child pediatric visits may be most effective (Table 1).

Organization of Care

From a health system perspective, available data support the contention that burns are most cost-effectively managed in dedicated burn centers rather than in general hospitals, (4) with improved survival in higher-volume centers. (5) Itemized in Table 2, the American Burn Association burn center transfer criteria have been widely disseminated and largely implemented in the United States. (6) From the perspective of the individual patient with severe and/or large burns, a highly organized process of burn management is ideal. This process can be described with 4 clinical phases: evaluation and resuscitation, initial excision and closure, definitive wound closure, and rehabilitation-reconstruction. (7)

PHYSIOLOGY OF BURN INJURY

Burn wounds trigger stereotypical local and systemic physiologic aberrations that increase in intensity with wound size and depth. Systemic changes are minimal when total burn size is small, meaning less than approximately 10% of the body surface. As burns become larger, systemic effects can become very significant.

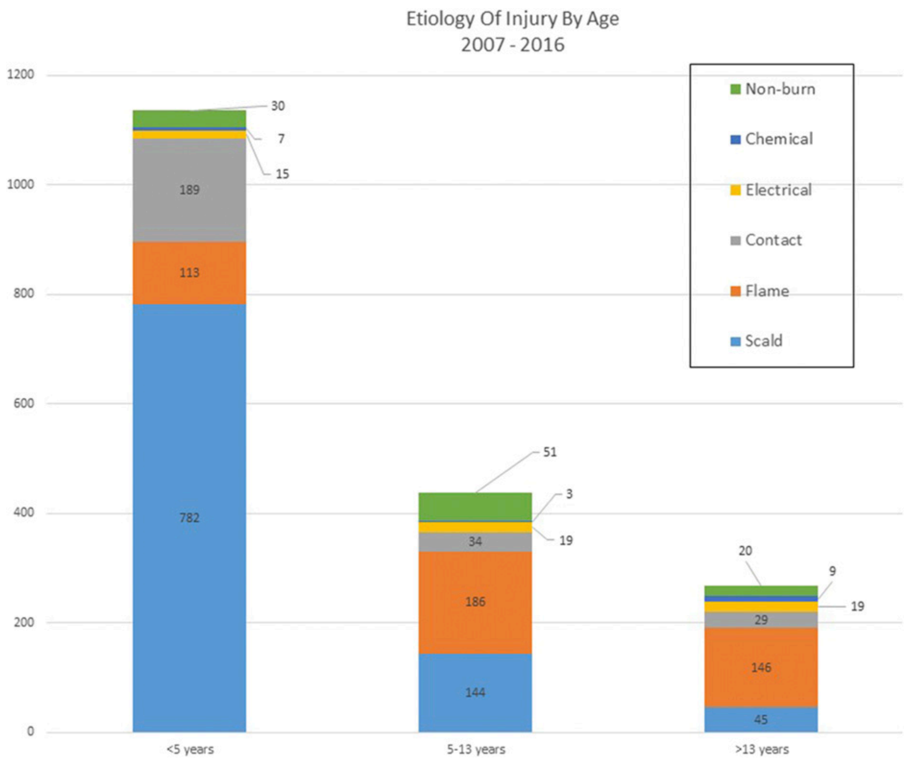


Figure 1. Age group versus mechanism of injury—Boston Shriners burn admissions over a 10-year period (2007–2016). In developed countries, infants and toddlers are particularly vulnerable to burn injury, most commonly by scalding in bath and kitchen incidents.

TABLE 1. **Selected Elements of Burn Prevention Counseling**

• Do not let cooking appliance electric cords hang off a counter.
• Do not leave hot beverages or foods unattended or near the edge of a table where a curious child can reach them.
• Keep hot beverages away from children and do not have a child sit in your lap while you drink a hot beverage.
• Teach older children how to safely remove hot food from a microwave or stove top.
• Minimize use of front burners on stoves so curious children cannot pull down pots of hot liquid.
• When carrying hot foods in the kitchen, ensure children are not in the path of movement.
• Test bathwater and shower temperature with your hand for 30 seconds.
• Never leave children unattended in the bath or shower.
• Adjust water heater so that the hottest temperature at the faucet is <120°F.
• Avoid leaving unattended pots on a stove.
• Keep children away from fireplace and wood stove doors with appropriate guards.
• Install smoke detectors on every floor of a dwelling and test them monthly. They are ideally hard-wired with battery backup. Batteries should be replaced at least annually on a schedule.
• Practice home fire drills and make sure children know how to exit the house and where to meet outdoors.
• Keep fire extinguishers in the kitchen, in the furnace room, and near a fireplace.
• Teach children to exit the house low to the floor if there is smoke in a room.
• Obtain a safety ladder if your home has a second story.
• Teach children who live in tall buildings not to use the elevator during a fire.
• Teach your children to "stop, drop, and roll" if clothing is on fire.
• Avoid smoking indoors.
• Minimize storage of flammable liquids and keep them away from areas where children can play and away from any ignition sources.
• Minimize use of extension cords.
• Keep matches and lighters where they will not be available to children.
• Avoid use of fireworks.

Local Response

In addition to direct coagulation of skin and subcutaneous fat, the local response to burn includes microvascular vasoconstriction and thrombosis in peripheral unburned tissue (8). This microvascular injury with secondary capillary thrombosis and necrosis explains, in part, the common clinical observation that burns appear to deepen in the days after initial evaluation. The degree to which progressive necrosis will occur is difficult to predict in individual patients. However, the process is thought to be exacerbated by long periods of hypotension, hypothermia, and wound infection. (9) This is an important consideration during the initial evaluation of children with extensive partial-thickness (second-degree) burns. Several devices designed to facilitate earlier determination of the likelihood that a burn will heal have been tested, but none have proved accurate or simple enough to be universally adopted. (10)

Systemic Response

The systemic response to a burn results from the body's response to a complex array of changes and insults, which can include neurohormonal changes, fluid loss, hypoproteinemia, and hypotension. (11) In children with large burns, the systemic response to burns can manifest as high fever and multi-organ dysfunction without infection. During the first 1 to 2 days after a larger injury, a hypodynamic state with decreased cardiac output and metabolic rate is common. (12) Subsequently, hypermetabolic physiology follows, with rising energy expenditure and cardiac output. This response is proportional to burn size, peaking at about twice the normal metabolic rate in

TABLE 2. **American Burn Association Burn Center Transfer Criteria**

- Second- and third-degree burns >10% TBSA in patients <10 or >50 y of age.
- Second- and third-degree burns >20% TBSA in other age groups.
- Second- and third-degree burns that involve the face, hands, feet, genitalia, perineum, and major joints.
- Third-degree burns >5% TBSA in any age group.
- Electrical burns, including lightning injury.
- Chemical burns.
- Inhalation injury.
- Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality.
- Any patients with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be treated initially in a trauma center until stable before being transferred to a burn center. Physician judgment will be necessary in such situations and should be in concert with the regional medical control plan and triage protocols.
- Hospitals without qualified personnel or equipment for the care of children should transfer children with burns to a burn center with these capabilities.
- Burn injury in patients who will require special social/emotional and/or long-term rehabilitative support, including cases involving suspected child abuse, substance abuse.

TBSA=total body surface area.
(Based on American Burn Association burn center referral criteria available at at http://ameriburn.org/wp-content/uploads/2017/05/burncenterreferralcriteria.pdf.)

children with burns involving more than half of the body surface. (13) This later response has important nutritional implications, including enhanced gluconeogenesis, insulin resistance, and increased protein breakdown. (14) A variety of pharmacologic agents have been used in clinical trials to reduce the impact of increased metabolism after large burns, including insulinlike growth factor, growth hormone, anabolic steroids, nonsteroidal anti-inflammatory agents, and β-antagonists. (15) All of these substances will improve protein catabolism, particularly anabolic steroids, but in most well-nourished children, sufficient nutritional support is adequate to address these changes. (16)

Unique Anatomical and Physiologic Concerns

Several important points regarding pediatric anatomy and physiology relevant to the treatment of burns are worth noting. (17) The small diameter of the child's airway makes occlusion by edema more likely, mandating more liberal use of prophylactic intubation, as indicated for head and neck swelling in the presence of stridor or retractions. Endotracheal tube security is of paramount importance. The trachea is shorter and more susceptible to right mainstem bronchial intubation. Young infants may have less mature renal concentrating ability and thereby require somewhat more fluid per unit body weight than older children (18); however, overreplacement of fluid may lead to fluid overload, so careful monitoring is advised. Hypotonic fluids are best avoided initially because seizures may occur in young children secondary to acute hyponatremia. For a given body weight, children have higher energy needs than adults and can quickly become catabolic, so early nutritional support is advisable. Children have a relatively large surface area to mass ratio, making them more susceptible to hypothermia, a constant consideration during early care. Similar to the elderly, infants and toddlers have relatively thin skin, making burns more likely to be full-thickness and donor sites more difficult to harvest and heal. Vascular access is more challenging in children as a result of their smaller blood vessels. Growing young children will frequently require revision of an initially good surgical result because burns and skin grafts often do not keep pace with skeletal growth. This mandates close long-term follow-up, rehabilitation therapy, and staged surgical revisions. Members of the child's extended family and school play a central role in injury recovery for children, so family and social support should be a part of recovery planning. (19)

INITIAL EVALUATION AND IMMEDIATE MANAGEMENT

Regardless of injury severity and mechanism, children with burns should be initially evaluated in an organized manner that includes primary and secondary surveys as outlined in the Advanced Burn Life Support course of the American Burn Association (20) and the Advanced Trauma Life Support approach of the American College of Surgeons. (21)

Primary Survey

The integrity of the airway is the highest-priority issue. Not all children who experience inhalation injury will require intubation. However, if they show signs of hoarseness, stridor, or progressive facial edema, intubation may be advisable, especially in smaller children. Ensuring that the endotracheal tube is secure is important and can be done with a variety of techniques, including a tie-harness. Uncuffed endotracheal tubes are ideally avoided because problematic air leaks can occur if respiratory failure develops and higher inflating pressures are required. (22) Secure vascular access should be obtained before long distance transport of children with major burns. If peripheral or central venous access is difficult, intraosseous access may be a good option. Short-term placement of intravenous or intraosseous lines through burn wounds is acceptable if required initially.

Secondary Survey

An organized secondary survey facilitates cataloging all aspects of a child's injuries, minimizing the potential for delayed care of injuries missed by an initial cursory examination. (23) The secondary survey includes a review and clarification of the mechanism of injury, a careful head-to-toe physical examination, and radiographs as directed by history and examination findings. Child abuse or neglect should be considered when presentation for care is delayed or the reported injury mechanism is not consistent with the physical findings. Some wound patterns are particularly concerning, such as those including flexor sparing and wounds consistent with immersion or contact (Fig 2). Hospital admission is advisable regardless of injury severity in such situations. A nonjudgmental history and a careful burn diagram are important components of documentation. Wound photography is particularly useful. (24)

Initial Evaluation of the Wound

In most children who present with a burn injury, the wound is their central problem, and an accurate determination of wound size and depth is the cornerstone of therapeutic decision making. Generally speaking, first-degree burns are dry and painful, second-degree burns are moist and painful, third-degree burns are dry and insensate, and fourth-degree burns demonstrate injury to underlying muscle and bone (Fig 3). Burn depth is difficult to ascertain accurately on early examination. It is often underestimated initially because the full extent of skin necrosis may take a few days to manifest (Fig 4). Deciding whether a wound will need surgery can be a difficult and important decision when caring for young children with mixed-depth burns. Because body proportions change with age, evaluation of burn size should include use of anthropometric diagrams such as the Lund-Browder diagram (Fig 5). The area of irregular nonconfluent burns can be estimated knowing that the palmar surface of a child's hand is approximately 1% of their body surface area. (25) It is particularly important to note burns that encircle or nearly encircle an extremity or the entire torso because monitoring distal to the burn for turgor and perfusion is often prudent.

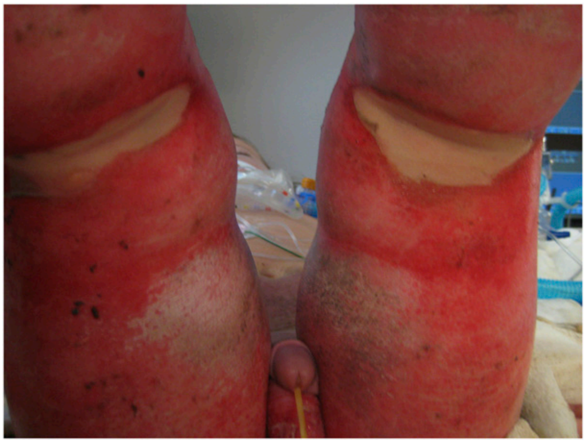


Figure 2. Abuse or neglect must always be considered during the initial evaluation. This burn pattern demonstrates flexor sparing of the popliteal fossa, concerning for possible immersion injury.

Initial Care of the Wound

Initial wound evaluation and debridement can be uncomfortable and scary for young children, who may require distraction in addition to analgesic and anxiolytic medications. Ketamine sedation can be particularly useful in children with larger wounds. (26) Unduly prolonged wound exposure should be avoided to minimize stress, desiccation, and wound contamination. Tetanus immune status should be ensured, especially if wounds are large or contaminated.

Decompression Procedures

In tissues confined by inelastic circumferential eschar or muscle compartments, progressive soft-tissue edema can

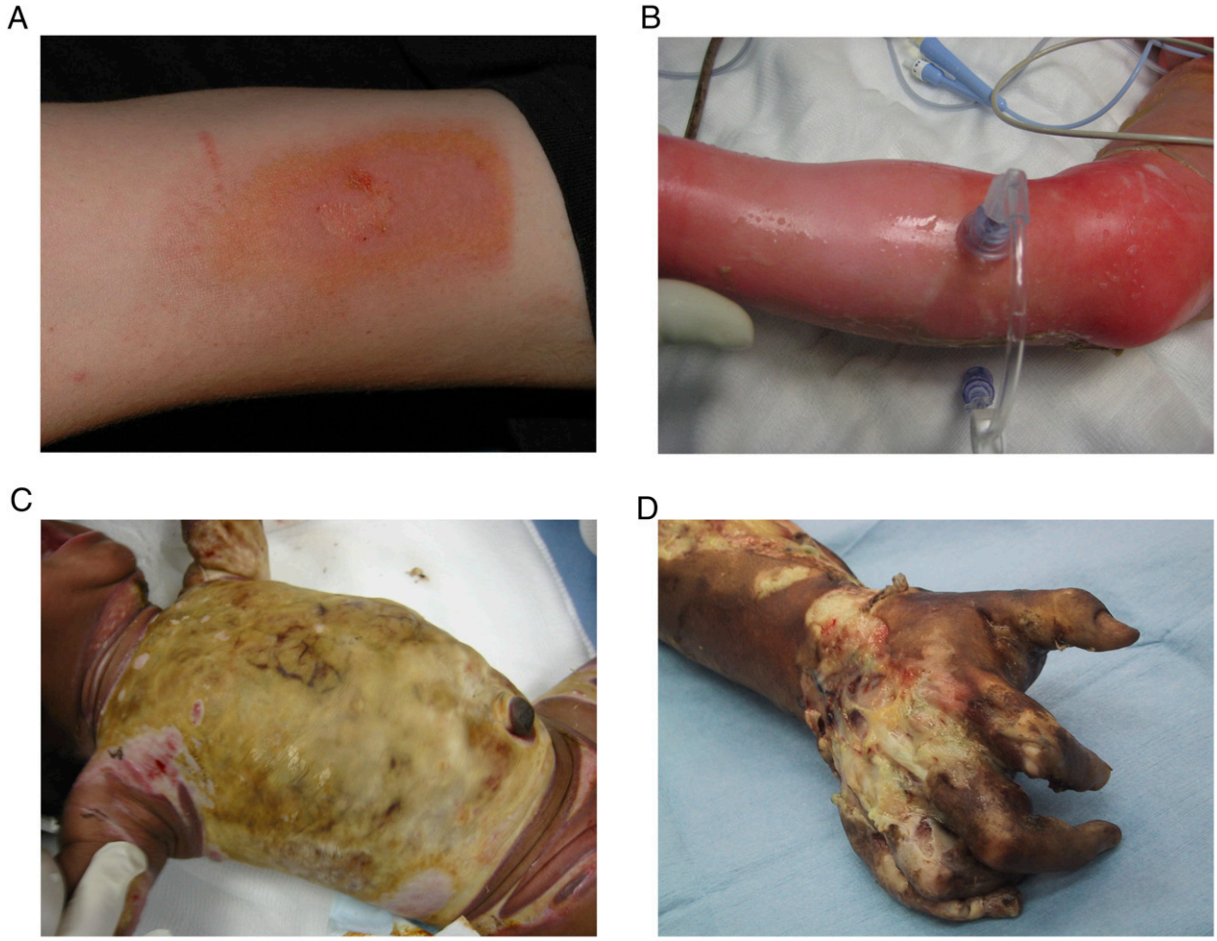


Figure 3. Burn depth can be deceiving on initial examination, but as a general rule, first-degree burns are dry and painful (A), second-degree burns are moist and painful (B), third-degree burns are charred and insensate (C), and fourth-degree burns appear to involve muscle and bone (D). Treatment planning depends in large measure on an initial estimate of burn depth.

drive up pressure, restricting blood flow and causing peripheral nerve ischemia and even muscle necrosis. This can be an issue even when burns are small if they are deep and near-circumferential. Early signs and symptoms of so-called compartment syndrome are easy to miss in children. Identification of extremities at risk for compartment syndrome with frequent focused reassessment will facilitate timely decompression before complications arise. When necessary, torso escharotomies can facilitate ventilation and improve renal perfusion and venous return from the lower body. Escharotomies can often be comfortably performed at the bedside with intravenous sedation using ketamine.

MANAGEMENT OF SMALL BURNS

Most burns in children are small and well managed in the outpatient setting. Even children whose burns have a deeper component who will need grafting may receive the bulk of their care as outpatients, often as a collaborative effort between their primary care pediatrician and regional burn unit. Ideally, there is a seamless interface between the inpatient burn unit and outpatient burn clinic, with nearly continuous access to both an inpatient and outpatient team.(27)(28)

Patient Selection

Careful patient selection will increase the chances that outpatient burn care is successful. Important considerations are listed in Table 3. There should be no concern for concomitant trauma, abuse, or neglect. There should be no concern for evolving airway edema. The burn should not be so severe as to warrant the child receiving a fluid resuscitation or monitoring. The child should not have difficulty drinking fluid. Children who potentially have deeper burns of critical areas such as the face, hands, feet, and genitals may be best managed initially as inpatients until burn depth is clear, pain is well controlled, and

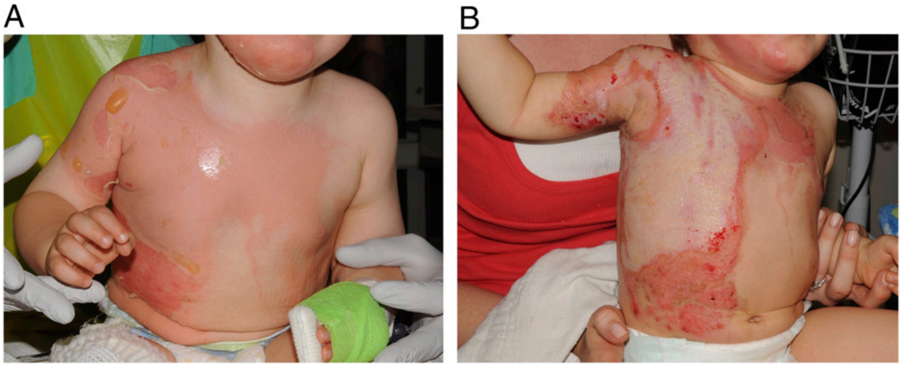
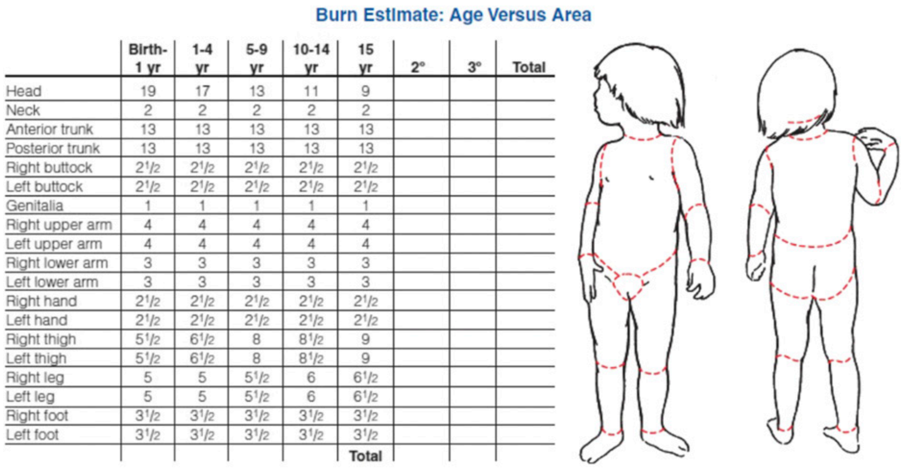


Figure 4. Burns commonly appear more superficial on initial presentation than they actually are. As shown here, there was significant change in wound appearance in this hot water scald between day 1 (A) and day 6 (B) This progression is not always easy to predict, but it is almost always to a deeper injury than initially apparent.

follow-up and wound care plans are established. The child's family should be able to support the child's wound care, monitoring, and transportation needs. If a child has circumferential wounds with risks of subeschar edema and distal ischemia, he or she should be monitored as inpatients until any risk of ischemia has passed. Small deep wounds that clearly need grafting should be surgically addressed promptly, sparing the child and family a prolonged outpatient prelude to surgery.

Outpatient Wound Care

Initially, wounds should be gently cleansed of debris and loose skin using clean (not sterile) technique with clean lukewarm tap water and bland soap. In most cases, blistered skin is gently removed. However, if blisters are intact and thick, and not tense or painful, and follow-up will be frequent, it is reasonable to simply monitor them. Some providers advocate blister drainage, allowing collapsed blistered skin to serve as a biologic dressing. Wounds should be kept clean, with periodic inspection and removal of fibrinous debris and any accumulated topical agent. Parents should be taught signs of infection (fever, malaise, or site erythema, swelling, and drainage) and told to return immediately if concerning signs are noted. Burn dressings prevent wound desiccation, decrease pain, reduce bacterial colonization, and minimize mechanical trauma. Topical antimicrobial ointments and gauze or one of the newer silver-releasing dressings can be effective. In most children, adequate pain control does not require narcotics. Elevation of the burn site above the heart reduces edema and helps with pain control. Creative collaboration with local medical and visiting nurse resources, community health programs, and family is useful in nearly every situation.



Burn Estimate: Age Versus Area

	Birth-1 yr	1-4 yr	5-9 yr	10-14 yr	15 yr	2°	3°	Total
Head	19	17	13	11	9			
Neck	2	2	2	2	2			
Anterior trunk	13	13	13	13	13			
Posterior trunk	13	13	13	13	13			
Right buttock	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$			
Left buttock	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$			
Genitalia	1	1	1	1	1			
Right upper arm	4	4	4	4	4			
Left upper arm	4	4	4	4	4			
Right lower arm	3	3	3	3	3			
Left lower arm	3	3	3	3	3			
Right hand	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$			
Left hand	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$	$2\frac{1}{2}$			
Right thigh	$5\frac{1}{2}$	$6\frac{1}{2}$	8	$8\frac{1}{2}$	9			
Left thigh	$5\frac{1}{2}$	$6\frac{1}{2}$	8	$8\frac{1}{2}$	9			
Right leg	5	5	$5\frac{1}{2}$	6	$6\frac{1}{2}$			
Left leg	5	5	$5\frac{1}{2}$	6	$6\frac{1}{2}$			
Right foot	$3\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$			
Left foot	$3\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$	$3\frac{1}{2}$			
					Total			

Figure 5. Because body proportions change with age, evaluation of burn size should include use of anthropometric diagrams, such as the Lund-Browder diagram. (Reprinted with permission from McInerny TK, Adam HM, Campbell DE, DeWitt TG, Meschan Foy J, Kamat DM *American Academy of Pediatrics Textbook of Pediatric Care*. 2nd ed. Elk Grove Village; American Academy of Pediatrics; 2017: 2428.)

TABLE 3. **Suggestions for Outpatient Burn Management**

Patient Selection Suggestions
• Airway is clear
• Burn small enough that fluid resuscitation not needed
• Child can eat and drink
• Family support adequate to meet monitoring, wound care, and transportation needs
• Family clearly understands care plan and follow-up recommendations
• No concern for abuse or neglect
Wound Care Suggestions
• Debride loose tissue and debris
• Gently debride leaking, loose, or thin blisters
• Apply antibiotic ointment or silver-releasing membrane based on local experience and protocols
• Schedule periodic inspections of the wound at 24 to 72 h; consider a pain control plan that minimizes opioid use
• Describe specific reasons for early return to family
• Schedule and track clinic visits
• Consult liberally with supporting inpatient burn facility
• Use local visiting nurse and outpatient medical support resources

Burns appropriate for outpatient care can generally be expected to heal within 3 weeks. Infection, most commonly cellulitis, is infrequent but should prompt immediate evaluation and antibiotic therapy. Infection most commonly occurs during the first week after injury. Prophylactic antibiotics are not routinely advised. (29) A 24-hour ability to contact the burn program is important should problems arise in the outpatient setting.

The most common clinic scenario involves a small scald burn that appears second degree on initial inspection. There are innumerable successful methods of managing such injuries. This author's usual practice is as follows. Using clean technique, initial wound examination and debridement are performed with distraction. Wounds are gently cleansed with saline and thin blisters removed. Normal distal perfusion and capillary refill are noted if relevant. Wounds are dressed with an antibiotic ointment (such as bacitracin, assuming no allergies) and gauze or a silver-releasing membrane. Assuming there are no indications for admission, a follow-up examination is planned for 24 to 72 hours later. At that time, real burn depth is usually apparent (burns very often appear more superficial on early examination than they actually are). Gentle cleaning is performed. If the wound still appears second degree, a similar antibiotic ointment dressing or a silver-releasing membrane is applied, and repeated examination is scheduled for 48 to 72 hours later. Families are taught how to replace the dressing. Visiting nurse or local pediatric resources may be engaged. Families are told that if fever, malaise, malodor, drainage, swelling, or increased pain occur, they should not wait for their scheduled follow-up but return immediately. Most children do not require narcotics in this setting because the ointment or membrane dressings provide significant comfort.

MANAGEMENT OF LARGE BURNS

Referring children with large burns (>20% of the total body surface area [TBSA]) to pediatric burn centers enhances survival. (5) Burn centers strive to deliver in 1 location a comprehensive package of care that meets all the needs of the burned child, from wound closure through emotional and social recovery.

Patient-Centered Care of Large Burns

An organized approach to the care of children with large deep burns will optimize outcome. The overarching focus is to achieve prompt closure of large deep wounds to avoid lethal sepsis and chronic painful and debilitating granulating wounds. General aspects of such an approach are outlined in Table 4. For greater detail of the medical and surgical approach to such children, the reader is referred to other resources. (30)

Fluid Resuscitation

In children with burns covering less than approximately 15% of the TBSA, metabolic changes tend to be limited, clinically significant capillary leak does not develop, and fluid resuscitation is generally unnecessary. Such children can usually be managed with fluid administered at 150% maintenance requirements by the oral and/or intravenous route while hydration status is monitored by physical examination and weighing diapers or measurement of urine output. Children with burns covering more than 15% of TBSA usually develop a diffuse capillary leak requiring resuscitation. Fluid resuscitation needs increase with burn size, burn depth, vapor transmission characteristics of the wound, inhalation injury, concomitant trauma, resuscitation delay, and other factors.

Each child presenting with a severe burn wound has unique resuscitation needs; formulas derived for quick calculation of fluid requirements provide only a rough approximation of actual requirements. Meeting these needs accurately requires that each child be approached as an individual, with careful tracking of response and adjustment of infusions as indicated. Careful bedside monitoring with titration of infusions usually results in a resuscitation that meets the child's individual physiologic needs accurately. (31)

TABLE 4. **Organizational Scheme for the Care of Large Burns**

PHASE	MAJOR OBJECTIVES
1: Initial evaluation and resuscitation	• Identification of all injuries • Completion of individualized fluid resuscitation • Liberal decompression of tight compartments to optimize perfusion and ventilation
2: Initial excision and biologic cover	• Clear identification and excision of deep burns • Biologic closure of resulting wounds
3: Definitive wound closure	• Replacement of temporary membranes with permanent grafts • Closure of complex deep wounds of face, hands, feet, genitalia
4: Rehabilitation, reconstruction, reintegration	• Initiation of program of passive joint movement, splinting, and antideformity positioning • Progression to an active joint movement and strengthening program • Initiation of scar management program • Fostering emotional health and community reintegration

Crystalloid-based burn fluids for burn resuscitation are effective in reversing burn shock but are associated with significant anasarca, which contributes to compartment syndromes, abdominal hypertension, airway compromise, and pulmonary dysfunction. (32) Traditional crystalloid-based resuscitation practice is perhaps best represented by the Parkland formula, which recommends administration of 4 mL of fluid per kilogram of body weight per percent surface area burn over the first 24 hours after injury, (2) with the first half of this volume given in the first 8 postinjury hours. Although meeting hemodynamic needs, this amount of fluid can be associated with anasarca in some children with larger burns. (33) In recent years, many providers are more often using early colloid in burn resuscitations. (34) Although this remains an area of controversy, it is the author's routine practice to administer 5% albumin at a maintenance rate in children with burns over 30% of the body surface, while subtracting this amount from calculated crystalloid needs. If children have burns covering more than 50% of TBSA, the author recommends administering twice the maintenance requirements of fluid as 5% albumin (Table 5).

During the first 24 hours of resuscitation of a child with a large burn covering more than 30% of TBSA, serum electrolytes tend to become similar to lactated Ringer solution because infusion rates are so high. Serum concentrations of potassium, ionized calcium, and magnesium may need to be corrected during resuscitation of children with such large injuries.

Inhalation injury, very deep burns, and delay in resuscitation will predictably increase resuscitation volume requirements. Although very small children with immature renal-concentrating abilities need more fluid per unit body weight than older children, they are often fluid overloaded if urine output targets are set too high. A urine output of 2 mL/kg per hour is not needed by most children. Even in mature infants, 0.5 to 1 mL/kg per hour generally suffices as a resuscitation end point.

Enteral fluid resuscitation of children with midsize burns is an option in austere or disaster situations. (35) An enteral fluid resuscitation plan can be calculated similar to an intravenous resuscitation plan, with fluid administered by gastric tube infusion or by frequent coached drinking.

Pediatric Burn Critical Care

An embedded pediatric critical care capability is necessary for pediatric burn programs. This can be accomplished either by a surgeon-run burn-specific ICU or through close

TABLE 5. **Author's Fluid Resuscitation Practice: Initial Infusions**

BURN SIZE, %	LR	5% ALBUMIN
1–20	1.5M	None
>20–50	P < 1M	1M
>50	P < 2M	2M

LR=lactated Ringer, M=calculated maintenance rate, P=Parkland calculation for crystalloid (4 mL/kg/%burn in first 24 hours, half in first 8 postinjury hours—typically 0.25 mL/kg/%burn/h for the first 8 hours).

Additional Points

1. *During the first 24 hours, the infusion rate is titrated hourly to physiologic end points. For the first 24 hours, LR solution is titrated. At 24 hours, LR solution and albumin are titrated in tandem. Typically, patients are requiring approximately 1.5M at 24 hours.*
2. *If the patient is a child weighing less than 20 kg, 1M of initial LR solution is provided as 5% dextrose in LR, and the reminder as LR solution.*
3. *If needed, boluses are given as 10 mL/kg of 5% albumin.*
4. *The goal is to be "just on the dry side of euvolemia."*
5. *Tube feedings can be started at a trophic rate during the first 24 hours in stable patients with monitored advancement. The tube feeding rate is subtracted from the LR solution rate.*
6. *Resuscitation end points include a comfortable but easily arousable mental status, warm distal extremities, systolic blood pressure greater than 60 mm Hg in infants and 70 to 90 mm Hg plus 2 times age in years for older children, pulse of 80 to 180 beats/min, urine output of 0.5 to 1 mL/kg per hour, and base deficit less than 2.*

collaboration with a general PICU. Continuous coordination and communication among all members of the burn team, including nurses, pediatricians, psychologists, anesthesiologists, intensivists, child life therapists, surgeons, and rehabilitation therapists, is essential for success. Severely burned children present a few unique issues to the critical care team.

Secure placement of the endotracheal tube can be more difficult to maintain in children with facial burns. Edema can make reintubation after unplanned extubation incredibly difficult. Both issues highlight the importance of vigilant attention to endotracheal tube security, which can be maintained using a tie-harness system. Early tracheostomy for children requiring intubation has been advocated, (36) but fairly long-term oral intubation can be associated with good outcomes while avoiding short- and long-term complications associated with tracheostomy. (37)

Children with serious burns experience a level of pain and anxiety unmatched in most any other disease processes. Tachyphylaxis to usual doses of opiates and benzodiazepine is routine. Significant dose escalation and use of additional agents such as dexmedetomidine are often required. (38) Proper control of this extraordinary pain and anxiety can benefit the child from a physiologic as well as an emotional perspective. Reduced catecholamine secretion can reduce systemic hypermetabolism. Control of pain and anxiety can have positive long-term emotional implications. (39)

Children with severe burns rapidly develop a catabolic hypermetabolic physiology that requires support. Tube feedings should be started concomitantly with fluid resuscitation unless children are hemodynamically unstable. In children who are not tolerating enteral feedings because of sepsis or for whom enteral feeds are contraindicated, short-term parenteral nutrition is well tolerated and can be particularly useful in young burn victims who are in a hypermetabolic state and, therefore, cannot tolerate prolonged fasts. (40) General consensus recommendations include nutritional goals of 2 to 2.5 g/kg per day of protein with a caloric target of 1.5 to 1.7 times a calculated basal metabolic rate or 1.3 to 1.5 times a measured resting energy expenditure. (41) The role of anabolic agents in children with burns is a long-standing area of controversy in the field and remains a program-specific practice. In most children, accurate enteral support will suffice to maintain lean body mass through the challenge of catabolic burns. (16)

Young children with burns have a propensity to develop high fever, even in the absence of systemic infection, while at the same time sepsis remains a major source of morbidity and mortality. (42) This concern results in a frequent treatment conundrum as clinicians struggle to determine whether a febrile burned child is infected and requires antibiotic treatment. General physical examination and wound evaluation should guide initial therapy. If hypotension or lethargy or other obvious signs of infection are present, bacterial cultures should be taken and broad spectrum antibiotic therapy started. Culture results with antibiotic sensitivities will allow for narrowing of bacterial spectrum coverage. In the absence of concerning findings, vigilant monitoring without antibiotic initiation is appropriate.

Inhalation injury also remains an important source of morbidity and mortality in burned children. Management strategies include airway protection from upper airway edema, vigilant pulmonary hygiene for removal of sloughed endobronchial debris, and accurate specific treatment of pulmonary infection. (43)

Historically, young age was an independent predictor of mortality from burns. However, with the evolution and application of pediatric critical care techniques to burned children, mortality has been sharply reduced, and young age is no longer a predictor of mortality. (44)

TABLE 6. **Important Considerations in Nonburn Conditions Commonly Referred to Burn Units for Definitive Care**

NONBURN CONDITION	CLINICAL IMPLICATIONS	COMMON TRAPS
Toxic epidermal necrolysis	Diffuse progressive cutaneous and visceral epidermal slough	Underappreciation of the trajectory of disease and involvement of visceral epithelium.
Staphylococcal scalded skin syndrome	Diffuse midepidermal cutaneous slough	Delayed realization of severity of illness and search for focus of colonization and antibiotic treatment.
Purpura fulminans	Diffuse small vessel thrombosis secondary to transient protein C deficiency associated with sepsis	Underappreciation of rapidity of disease progression and extent of soft tissue necrosis and debridement required.
Tar injury	Very hot and viscous agent adheres to skin	Delayed cooling of persistently hot viscous materials.
Chemical injury	Diffuse group of cutaneous and pulmonary injury	Underappreciation of effects of fumes on lungs and of systemic effects of absorbed chemical (notably hydrofluoric acid)
Electrical injury	Range of soft tissue injury with increasing voltage and contact duration and quality.	Underappreciation of occult cardiac and muscle injury, rhabdomyolysis, and secondary compartment syndrome.
Crush injury	Graded soft tissue, bone, and visceral injury with secondary consequences of edema and of reperfusion.	Underappreciation of injury severity with missed muscle ischemia due to primary ischemia and to reperfusion edema.
Blast injury	Graded injury severity (primary to quaternary injury patterns), occult visceral injury. Frequently associated with fragmentation injury.	Underappreciation of secondary, tertiary, and quaternary components of injury. Missed associated visceral injury.
Frostbite	Graded soft tissue ischemia secondary to small vessel thrombosis	Missed opportunities for thrombolytic therapy. Refreezing during transport.
Soft tissue infections	Rapidly spreading deep infection with systemic inflammation and sepsis	Underappreciation of rapidity of progression and extent of debridement required.

NONBURN PROBLEMS IN THE BURN UNIT

The burn unit has a unique set of resources that includes critical care, complex operative and nonoperative wound management, and rehabilitation. (45) This resource set is useful for a variety of medical and traumatic nonburn conditions that are commonly referred to burn units for management. (46) Conditions, clinical implications, and common traps are highlighted in Table 6.

RECONSTRUCTION, REHABILITATION, REINTEGRATION

With larger numbers of children surviving serious burns, an increasing focus has been directed toward long-term burn outcomes. Early data seem to indicate that with participation in comprehensive burn aftercare programs, even children with severe burns can enjoy a very satisfying quality of life. (47) Components of these programs include scar management, burn-specific physical and occupational therapy, ready access to burn reconstruction, emotional counseling, and family and peer support. (19) Facilitating access to effective burn aftercare and recovery tools represents a wonderful opportunity to improve the lives of children with burns after the acute treatment phase has passed. (48)

Summary

- Based on epidemiologic studies, burns are common injuries seen in most emergency and general pediatric practices. (1)(2)
- Observational studies demonstrate that serious burns are most successfully and cost-effectively managed in dedicated programs. (4)(5)
- Observational data demonstrate that burn injury causes a graded stereotypical set of physiologic changes. (12)(13) Initially a hypodynamic state is seen, requiring resuscitation for larger injuries. Subsequently, a hypermetabolic and catabolic state ensues. Observational studies suggest a benefit to nutritional support during this evolving physiologic process. (14)
- Observational studies and expert opinion suggest that patient selection, gentle wound care, and close follow-up are key principles of successful outpatient management (27) and that membrane dressings have a useful role. (28)
- Based primarily on consensus due to lack of relevant clinical studies, in recent years fluid resuscitation priorities have

included a more restrictive approach to volume administration and the more liberal use of colloid. (30)

- Based on expert consensus, the American Burn Association has promulgated a set of burn center transfer criteria that have been largely implemented in the United States. (6) Observational data demonstrate that referral of children with complex needs to regional burn programs for acute and collaborative aftercare is beneficial (4)(5) and that participation in burn aftercare programs is associated with enhanced physical and emotional outcomes. (19)(48)

References for this article are at http://pedsinreview.aappublications.org/content/39/6/273.

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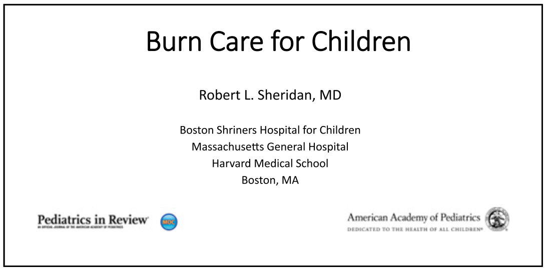

Burn Care for Children

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1. A 2-year-old boy sustains a 40% burn while participating in match play with older siblings. The child is airlifted to a regional burn center and undergoes resuscitation and initial debridement over the next 5 days. Enteral tube feedings were started 18 hours after admission. Today is day 9 after the injury. The child is not clinically septic. Which of the following physiologic responses is expected to be seen at this point in this patient?
   - A. Bradycardia.
   - B. High cardiac output.
   - C. High peripheral vascular resistance.
   - D. Hypothermia.
   - E. Relative hypothyroidism.
2. A 5-year-old girl takes a tumble into a recently extinguished campfire while camping with her family. She experiences contact burns from the scattered hot coals to both arms, both legs, portions of her anterior torso, and her right cheek. Which of the following is the most practical method to estimate her scattered nonconfluent burn size?
   - A. Estimate assuming the patient's palm is 1% of the body surface.
   - B. Measurement of each wound's dimensions using a measuring tape.
   - C. The Lund-Browder diagram with detailed drawings of each wound.
   - D. The pediatric "rule of nines."
   - E. Wound photography with use of a planimetry application.
3. A 12-month-old boy is badly burned when a cribside candle ignites his bedding. Burn size is estimated to be 65%, and all looks to be third degree. The face is involved. The child is transported to a local emergency department, arriving 20 minutes after injury. He is intubated, and central venous access is secured. A bladder catheter is placed. The child weighs approximately 10 kg. Which of the following is the most appropriate starting total initial (8 hours) hourly rate of resuscitation fluid in this patient?
   - A. 80 mL/h of 5% dextrose lactated Ringer (D5LR) solution.
   - B. 80 mL/h as D5 normal saline.
   - C. 110 mL/h of normal saline solution and 5% albumin.
   - D. 160 mL/h of D5LR solution, LR solution, and 5% albumin.
   - E. 160 mL/h of D5 normal saline.
4. The child in question 3 survives his injury. His acute burn care was provided at a regional pediatric burn unit 200 miles from his home. The burn team collaborates with his local pediatric practice to craft a comprehensive long-term aftercare program. Which of the following is not an essential component of a typical aftercare program?
   - A. Burn reconstruction.
   - B. Daycare placement requirements.
   - C. Emotional counseling and family and peer support.
   - D. Physical and occupational therapy.
   - E. Scar management.
5. A 3-year-old girl pulls a hot cup of coffee off the kitchen table onto her upturned lower face and anterior torso. She experiences approximately a 9% scald burn that is blanching and painful. Her lips are swollen and tender, but she has no intraoral blistering, and her airway seems clear. She will not drink. A peripheral intravenous line is started. Which of the following intravenous fluid regimens is the most appropriate to administer in this patient?

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A. 5% albumin solution at a maintenance rate.
B. D5LR solution at a maintenance rate with an additional half maintenance rate of LR solution without dextrose.
C. D5 in one-quarter normal saline at a maintenance rate.
D. LR solution at twice the maintenance rate.
E. Normal saline at a rate calculated by the Parkland formula.

Staphylococcus aureus

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Practice Gap

Staphylococcus aureus can cause numerous disease processes, and management varies with pathology and severity. It is important for the general pediatrician to identify factors that increase a patient's risk of developing *S aureus* infection to ensure appropriate treatment.

Objectives After completing this article, readers should be able to:

1. Understand the epidemiology of common *Staphylococcus aureus* diseases.
2. Recognize risk factors that increase patient susceptibility to *S aureus* infections.
3. Understand the difference in clinical presentations and pathogenesis between *S aureus* infection and toxin-mediated illness.
4. Understand the importance of bacterial cultures, antibiotic susceptibilities, and local community prevalence of methicillin and clindamycin resistance.
5. Identify which antibiotics are appropriate for empirical treatment of methicillin-sensitive and methicillin-resistant *S aureus.*
6. Understand the level of evidential support regarding decolonization practices and when such practices are recommended.

Abstract

Staphylococcus aureus is a bacterium that can cause a variety of illnesses through suppurative or nonsuppurative (toxin-mediated) means. *S aureus* is a common cause of skin and skin structure infections as well as osteoarticular infections in the pediatric population. *S aureus* is also identified in cases of septicemia, infective endocarditis, pneumonia, ocular infections, and central nervous system infections. To design appropriate empirical therapy, pediatricians should be knowledgeable about the resistance patterns of *S aureus* in their communities, including methicillin and clindamycin resistance. This article reviews the microbiology, colonization and transmission, and antibiotic resistance of and clinical diseases caused by *S aureus.*

AUTHOR DISCLOSURE Drs Ondusko and Nolt have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BLRBL	β-lactamase–resistant β-lactam
CA-MRSA	community-acquired methicillin-resistant *Staphylococcus aureus*
CNS	central nervous system
IE	infective endocarditis
IV	intravenous
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
PBP	penicillin-binding protein
SSSS	staphylococcal scalded skin syndrome
SSSI	skin and skin structure infection
TMP-SMX	trimethoprim-sulfamethoxazole
TSS	toxic shock syndrome
VISA	vancomycin-intermediate *Staphylococcus aureus*
VRSA	vancomycin-resistant *Staphylococcus aureus*

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CASES

1) *A 7-month-old boy, previously healthy, is seen in the emergency department with a 1-day history of rash, which had the initial appearance of a sunburn. Involved areas are now peeling. His parents describe him as being very fussy and having decreased number and volume of wet diapers. On physical examination he is afebrile, with a temperature of 99.5°F (37.5°C), heart rate of 164 beats/min, respiratory rate of 32 breaths/min, blood pressure of 72/46 mm Hg, and pulse oxygen saturation of 99% on room air. He has numerous bullae over his body and a positive Nikolsky sign.*

   Staphylococcal scalded skin syndrome (SSSS).

2) *A 12-year-old boy hospitalized for inflammatory bowel disease management has a central venous line for total parenteral nutrition. He suddenly develops a new fever (102.0°F [38.9°C]), is shivering, and complains of being "cold." Physical examination reveals a toxic-appearing boy who is febrile to 103.1°F (39.5°C) and has a heart rate of 126 beats/min, respiratory rate of 24 breath/min, blood pressure of 90/40 mm Hg, and pulse oxygen saturation of 98% on room air. The central line insertion site is without erythema or drainage. His examination reveals a new cardiac systolic murmur, tachycardia, and poor perfusion. Blood cultures are obtained from his central line as well as a peripheral venipuncture, and he is given intravenous (IV) antibiotics due to his toxic clinical appearance. Within 24 hours, blood cultures grow* S aureus. *The central line is removed and his antibiotics are appropriately tailored once antibiotic susceptibilities are available on the bacteria. However, he continues to have positive blood cultures for 5 days after removal of the central line and appropriate antibiotic therapy. Due to his new cardiac murmur and the persistence of positive blood cultures, an echocardiogram is performed and a large thrombus is detected on his tricuspid valve.*

   Bacteremia and infective endocarditis (IE) with a central line.

3) *A 3-year-old toddler, previously healthy with normal growth and development, is seen for an urgent visit for a chief concern of limping for 2 days. He is usually a very active child and plays and runs around the house in the morning with his siblings. This morning he woke up and refused to walk or play. In the clinic, he is febrile to 101.5°F (38.6°C), heart rate of 130 beats/min, respiratory rate of 38 breaths/min, blood pressure of 80/56 mm Hg, and pulse oxygen saturation of 97%. On physical examination, the child is keeping his right leg abducted, flexed, and externally rotated. He refuses to move it from this position and does not allow you to move it passively. Imaging is obtained and shows an effusion of the hip. He is diagnosed as having septic arthritis and is taken to surgery.*

   Osteoarticular infection

BACTERIAL VIRULENCE FACTORS

To understand the basic hardiness and virulence of this bacterium, a review of the structure, extracellular products, and genetic elements is paramount. (1)

S aureus is a gram-positive bacterium that appears in clusters on Gram-stain. (1) It is catalase positive and, unlike other staphylococcal species, coagulase positive. (1) There are several methods to identify *S aureus*, eg, polymerase chain reaction and peptide nucleic acid fluorescence in situ hybridization, although the best known and most used is the bacterial culture. (2)

S aureus has a variety of virulence factors that, singly and in combination, can result in severe infection. Catalase, produced by *S aureus*, is an enzyme that allows intracellular survival of this bacterium by breaking down hydrogen peroxide, a host defense mechanism. (3) Surface proteins of *S aureus* include coagulase (the catalyst that generates fibrin from fibrinogen) and clumping factors (which cause clotting). (1) Toxins and extracellular substances include hemolysins (which destroy erythrocytes), leukocidins (which cause skin necrosis), and exfoliative toxin and enterotoxins B and C (which propagate the systemic inflammatory response). (1) Panton-Valentine leukocidin is a toxin that can do all the above. (4) These virulence factors allow *S aureus* to cause the variety of clinical syndromes for which this bacterium is known, including the development of abscesses.

S aureus can acquire new genetic elements. (1) Local environmental stressors, such as low pH, low oxygen, poor availability of nutrients, extremes in temperatures, and antibiotic use, may force altered genetic expression through regulatory mechanisms. (1) In total, intrinsic and acquired genetic material expands the ability of *S aureus* to affect the patient while surviving in harsh conditions.

RESISTANCE PATTERNS

S aureus has proved adept at developing antibiotic resistance. This is accomplished through acquisition of mobile genetic elements that transfer resistance and virulence from other bacterial species and staphylococcal strains. (1) External pressures (namely, overuse of antibiotics) can also force a previously susceptible isolate to become resistant.

The most well-known story of *S aureus* resistance follows the introduction of penicillin. *S aureus* developed resistance via production of β-lactamase, which prevents the antibiotic from binding to the penicillin-binding protein (PBP) on *S aureus*. This lack of binding to PBP obstructs the ability of the penicillin drug to inhibit bacterial cell wall synthesis. (1) This β-lactamase was not

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native to *S aureus*, it was acquired via a plasmid-encoded penicillinase. (1)(5)

The evolution of methicillin resistance should be familiar. Semisynthetic penicillins (the prototype being methicillin) were developed by scientists to circumvent the problem of *S aureus* β-lactamase resistance. However, shortly after the introduction of these compounds, some *S aureus* strains became methicillin resistant. Methicillin resistance was acquired via the *mecA* gene encoding for PBP2a, which decreases the binding affinity of antibiotics to the target bacterium. (5)(6) It is proposed that *S aureus* acquired the *mecA* gene from other staphylococcal species. (6)

An ominous example of acquisition of resistance pertains to vancomycin, regarded by medical providers as a workhorse against gram-positive pathogens. Vancomycin-intermediate *S aureus* (VISA) was identified in the 1990s. Although the resistance mechanisms of VISA are not completely understood, the result is a minimum inhibitory concentration (MIC) of vancomycin greater than or equal to 4 μg/mL to overwhelm *S aureus* (the usual MIC is <2 μg/mL). (1) Vancomycin-resistant *S aureus* (VRSA) is defined as possessing a MIC for vancomycin that is greater than or equal to 16 μg/mL. (1) The first case of VRSA was reported in 2002. The resistance of VRSA is attributed to the *VanA* gene, which was acquired from enterococcus, an entirely different bacterial genus. (1)

The susceptibility of *S aureus* isolates to clindamycin is variable. The provider should be aware that methicillin-sensitive *S aureus* (MSSA) and methicillin-resistant *S aureus* (MRSA) isolates may be intrinsically resistant to clindamycin or resistance may be inducible. The latter is suspected if there is discordance in a laboratory result: clindamycin-susceptible but erythromycin-resistant *S aureus*. (2) In this situation, the laboratory will conduct a procedure on the bacteria known as the D test. (2) In the case of a positive D test result (inducible clindamycin resistance), an alternate drug is used. A study from found MSSA and MRSA clindamycin-resistance rates as high as 32.7% and 90.8%, respectively. (7) In 1 study using a multihospital database in the United States from 2007 through 2011, 24,644 clinically relevant *S aureus* isolates were reported. Of those that had clindamycin susceptibility testing completed, 39.1% to 40.4% were clindamycin resistant (the authors did not distinguish between MRSA and MSSA). (8)

Knowledge of community antibiotic resistance patterns to *S aureus* should guide empirical antibiotics used to treat community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA. The latter is usually multidrug resistant, whereas CA-MRSA is often susceptible to clindamycin, doxycycline, and trimethoprim-sulfamethoxazole (TMP-SMX). (2) When confronted with suspected *S aureus*, providers should be aware of the proportion of CA-MRSA compared with MSSA in their community, and the resistance of the prevailing *S aureus* strains (especially against clindamycin). This information may be obtained by contacting local infectious diseases practitioners or the director of a local facility's microbiology laboratory.

COLONIZATION AND TRANSMISSION

Staphylococcus is considered a part of normal human flora termed *colonization*. A common body area of *S aureus* colonization is the anterior nares. An estimated one-third of the human population (including the pediatric population) has asymptomatic *S aureus* colonization. (2)(9)(10)(11) In 2016, among kindergarten attendees in Iran, 25% were colonized with MSSA and 6% with MRSA. (12) In a prospective study of children in St Louis with community-onset *S aureus* skin and skin structure infections (SSSIs), more than half of the patients were colonized with 1 strain, 44% with 2 strains, and 4% with 3 strains. (13) Therefore, it is not unusual for a pediatric patient to be colonized with *S aureus*, and to possibly harbor more than 1 *S aureus* isolate.

Colonization is a risk factor for infection, and infection often occurs with the same *S aureus* strain that colonized the individual. In the previously cited study from St Louis, 67% of children were colonized with the same strain of *S aureus* that caused their SSSI. (13) In a survey of outcomes of children in the 6 months after knowledge of *S aureus* colonization, SSSI developed in 23% of children colonized with MRSA, 8% of children colonized with MSSA, and 7% without evidence of previous colonization. (14)

Infections may not always result from the patient's colonizing *S aureus* strain. One prospective study determined that more than half of the *S aureus* SSSIs in children were caused by a strain with which the child was not colonized. (15) Asymptomatic colonized individuals may spread the organism to others. (11) Sources for noncolonizing strains include household contacts. However, 1 study demonstrated that less than half of the strains responsible for the infection were the same strain with which the patient or household contact was colonized. (2)(13)

SUPPURATIVE ILLNESSES

The pathologic development of the following suppurative infectious syndromes are similar regardless of causative bacterial agent. The discussion of illnesses later herein is summarized in Table 1. The provider should allow the severity of disease and the suspicion of MRSA to guide the choice of empirical antibiotics.

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TABLE 1. **Infectious Syndromes Caused by *Staphylococcus aureus* in Pediatrics**

INFECTIOUS SYNDROME	INCIDENCE/ EPIDEMIOLOGY	PATHOGENESIS AND/ OR RISK FACTORS	TREATMENT	TREATMENT IF HIGH CONCERN FOR MRSA	TREATMENT DURATION
SSI - mild	Roughly a third of the population is colonized with *S aureus*	Direct inoculation	Mupirocin 2% topical ointment	No change	7 days or guided by response to treatment
SSI - furuncles	Roughly a third of the population is colonized with *S aureus*	Direct inoculation	Application of moist heat. If unresponsive or large, incision and drainage ± antibiotics	No change	7 days or guided by response to treatment
SSI - other (including if systemic signs are present)	unknown	Direct inoculation	BLRBL	Vancomycin, clindamycin, linezolid, doxycycline, TMP-SMX	7 days or guided by response to treatment
Bacteremia	1.54–1.95 per 1,000 pediatric hospitalizations	Foreign body, respiratory, osteoarticular, or SSSI hematogenous spread of infection	BLRBL + vancomycin		Minimum 14 d after first negative blood culture
Infective endocarditis	0.41–0.43 per 100,000 children (*S aureus* 24%–36%)	Heart defect, foreign body, intravenous drug use	BLRBL + vancomycin ± gentamicin ± rifampin		2–8 wk after first negative blood culture
CNS infection	5%–6% of bacterial meningitis; ~23% of VP shunt infections	Direct inoculation, foreign body, midline spinal defect	Nafcillin/oxacillin + vancomycin		2 wk for meningitis; 4–8 wk for intracranial abscess
Pneumonia	1% of CAP requiring hospitalization; 6%–32% of necrotizing pneumonia	Inhalation, hematogenous seeding	BLRBL	Vancomycin, clindamycin,[b] linezolid	7 d or guided by response to treatment
Osteoarticular infection	7.1 per 100,000 children (overall, not specific to *S aureus*)	Hematogenous, direct inoculation, contiguous spread	BLRBL	Vancomycin,[c] clindamycin,[b] linezolid	3–4 wk for septic arthritis; 4–6 wk for osteomyelitis
Ocular infections	12.1% of ophthalmologic infections are caused by MRSA	Direct inoculation, contiguous and/or hematogenous spread	BLRBL	Vancomycin, clindamycin,[b] linezolid	2 wk

BLRBL=β-lactamase–resistant β-lactam, CAP=community-acquired pneumonia, CNS=central nervous system, MRSA=methicillin-resistant Staphylococcus aureus, *MSSA=methicillin-sensitive* Staphylococcus aureus, *SSSI=skin and skin structure infection, TMP-SMX=trimethoprim-sulfamethoxazole; VP=ventriculoperitoneal.*

[a] *Mild SSSIs include impetigo, localized folliculitis, and superficial secondary bacterial infection.*

[b] *Clindamycin may be considered if a high percentage of* S aureus *isolates in the community are susceptible to clindamycin.*

[c] *Vancomycin is included in the empirical treatment if community rates of MRSA are greater than 10%.*

Skin and Skin Structure Infections

One of the more common manifestations of *S aureus* is SSSI (previously named *skin and soft tissue infection*). (16)(17) Although 1 study reported an increasing rate of hospitalizations for pediatric SSSI over a 10-year period, only 20% of these were secondary to *S aureus*, including 10% from CA-MRSA. (18) Methicillin-resistant *S aureus* SSSI seems to be more prevalent in the late spring to late summer months. (18)(19) Thus, the provider should be aware that only a minority of SSSIs requiring hospitalization are caused by *S aureus* and that SSSIs secondary to MRSA may have a seasonal propensity.

In addition to nonintact skin being a risk factor for SSSI, an additional risk is seen in patients with atopic dermatitis. Atopic dermatitis is an inflammatory disorder of the skin, which

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increases the risk of developing secondary dermatologic (and other) bacterial infections from many organisms, but importantly from *S aureus*. Separate from its ability to cause infection, *S aureus* produces several toxins and proteins that impair the ability of regulatory T cells to suppress an overly active local immune reaction, thus allowing the local inflammatory response from atopic dermatitis to proceed. (20) Ways to reduce or eliminate *S aureus* bacterial burden (decolonization, described later in this review) become of greater importance in patients with inflammatory skin disorders, who may be at risk for not only infection by *S aureus* but also worsening of their underlying disease pathophysiology.

For mild skin infections such as impetigo, localized folliculitis, or superficial secondary bacterial infection, mupirocin 2% topical is appropriate treatment. (2)(21) Furuncles may respond by application of moist heat, which promotes suppuration. (21)(22) However, for larger furuncles or furuncles that do not spontaneously drain or decrease in size, incision and drainage is the treatment of choice. (21)(22)

Antibiotics may not provide additional benefits after incision and drainage. However, there are clinical scenarios in which a systemic antibiotic is indicated. (21)(23) Infection-related concerns include abscesses in multiple sites (extensive disease), abscesses that cannot be adequately drained, rapid progression of infection, associated septic phlebitis, or a lack of improvement or a recurrence after incision and drainage. (21) Patient factors that may prompt the use of systemic antibiotics include evidence of systemic illness (fever, hypotension), individuals at extremes of age, or those with comorbidities (diabetes mellitus, human immunodeficiency virus infection, immunocompromised status, and neoplastic disease). (2)(21) If possible, abscesses should be cultured before the initiation of antibiotic therapy. (21)

Appropriate treatment depends on whether the suspected or confirmed pathogen is MSSA or MRSA. Antibiotic treatment for MSSA includes a β-lactamase–resistant penicillin or, if allergic, a first-generation cephalosporin. (2)(21) If there is concern for MRSA (given community prevalence), TMP-SMX, doxycycline, clindamycin, or linezolid can be used for MRSA treatment. (2)(21) Purulent cellulitis should be treated empirically for MRSA until cultures result to guide treatment; duration is 5 to 10 days. (21) Trimethoprim-sulfamethoxazole should never be used as empirical monotherapy for cellulitis given the historically poor treatment of *Streptococcus pyogenes*. (2) Parenteral empirical MRSA treatment includes vancomycin, linezolid, or clindamycin. (21)

Bacteremia. The incidence of *S aureus* bacteremia has been reported to be 1.54 to 1.95 in 1,000 pediatric hospitalizations in the United States. (24)(25) Risk factors that increase the incidence of *S aureus* bacteremia include extremes of age (<12 months old), sex (males with slightly higher incidence), and ethnicity (higher rates in the African American population in the United States). (26)(27)

For *S aureus* bacteremia, a β-lactamase–resistant β-lactam (BLRBL) combined with vancomycin is the treatment of choice until guided by antibiotic susceptibility results. (2)(21) For uncomplicated bacteremia, the treatment duration is (minimum) 14 days after microbiological clearance. Complicated bacteremia includes metastatic spread (emboli to lungs, solid organ, or brain), IE, lack of defervescence within 72 hours of appropriate antibiotic treatment, persistently positive cultures after 2 to 4 days of appropriate treatment, presence of an implanted device(s), or recurrence within 3 months after completing therapy. (21)(26)(28) Duration of treatment may be extended for immunocompromised patients, those with catheter-related bacteremia, and those with complicated outcomes. (2) Expert consultation with an infectious diseases expert should be sought for treatment of complicated bacteremia.

Infective Endocarditis. Infective endocarditis is not as common in the pediatric population as in the adult population. In incidence studies, more than half of the cases of pediatric IE possess an underlying cardiac condition. (29)(30) The incidence of IE has not changed appreciably between the early 2000s and the 2010s, (0.41–0.43 per 100,000 children). The most common responsible organism was *S aureus*, accounting for 24% to 36% of IE. (26)(29)(30) So although IE is not common in pediatrics, the clinician should be aware that *S aureus* accounts for one-third of these infections.

For *S aureus* IE, vancomycin plus a BLRBL is the treatment of choice until guided by susceptibility results. For MSSA, a BLRBL (eg, nafcillin, oxacillin, or cefazolin) is the treatment of choice with the option of adding gentamicin for synergy for the first 3 to 5 days of treatment. (31) For MRSA, vancomycin is the treatment of choice, with or without gentamicin for the first 3 to 5 days of treatment. (31) If the patient has prosthetic material, rifampin and gentamicin should be added to the treatment regimen for the first 2 weeks. (21)(31) Consultation with an infectious diseases specialist is warranted in pediatric IE. Treatment duration is 2 to 8 weeks. (2)(21)(31) Infective endocarditis due to *S aureus* has a higher mortality rate (22%–66%) than other causes of IE. (26)

Infections of the Central Nervous System. *S aureus* is not a common cause of central nervous system (CNS) infection. (32)(33) Microbiological surveillance during 2004 to 2011 in a health-care system in England and Wales showed that *S aureus* accounted for 5% of bacterial meningitis in children younger than 14 years and 6% of bacterial meningitis in

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infants younger than 3 months. (34) A retrospective analysis from Korea analyzing outcomes of children with ventriculoperitoneal shunts revealed a rate of infection of 0.075 cases per shunt-year. (35) *S aureus* was the second most commonly identified organism (apart from coagulase-negative staphylococcus), accounting for 22.9% of ventriculoperitoneal shunt infections. (35) It is exceedingly rare for a child to develop an *S aureus* brain abscess solely from contiguous spread from sinusitis, without a preexisting bony defect. (36) In a child experiencing *S aureus* meningitis without a history of CNS trauma or procedures, a midline spinal defect (occult spina bifida) should be sought.

Foreign bodies (such as a ventriculoperitoneal shunt) will serve as a nidus of infection and should be removed. Any abscess or collection of infection in or near the brain warrants a surgical evaluation. (21) Empirical treatment of *S aureus* CNS infection is vancomycin with nafcillin or oxacillin. (2) Duration of treatment varies, from 2 weeks for meningitis to 4 to 8 weeks for intracranial abscesses. (21)(36)

Pneumonia. Compared with other bacteria, *S aureus* is a less common cause of pneumonia (community and hospital acquired). Active population surveillance for community-acquired pneumonia at 3 pediatric hospitals in the United States found that *S aureus* accounted for 1% of community-acquired pneumonia requiring hospitalizations. (37) Necrotizing pneumonia (destruction of lung parenchyma with vascular changes) is an uncommon but severe complication of community-acquired pneumonia. A retrospective study in Poland noted that necrotizing pneumonia in children accounted for 3% of all hospital admissions for pneumonia from 2008 to 2013. (38) *S aureus* is 1 of the recognized causative organisms of necrotizing pneumonia and accounts for 6% to 32% of all necrotizing pneumonia. (38)(39) A large proportion of *S aureus* isolates responsible for necrotizing pneumonia possess the gene for Panton-Valentine leukocidin (previously described in this review as a virulence factor). (39) Overall, *S aureus* is an uncommon cause of pneumonia, but the clinician should be aware of the ability of some strains of *S aureus* to cause necrotizing pneumonia.

The empirical treatment of pneumonia suspected to be from *S aureus* depends on severity of presentation and prevalence of MRSA. Pneumonia from MSSA should be treated with a BLRBL. Vancomycin remains the preferred empirical antibiotic for MRSA-suspected severe pneumonia, but it has relatively poor lung tissue penetration. (21) For MRSA pneumonia, clindamycin may be an adequate choice if the provider knows that a high percentage of *S aureus* isolates in the community are susceptible to clindamycin. (21) An alternative antibiotic for MRSA pneumonia (particularly if oral therapy is desired for a MRSA isolate that is clindamycin resistant) is linezolid. (21) Suggested duration of treatment for *S aureus* pneumonia is 7 days, although complications such as necrotizing pneumonia may prolong treatment.

Osteoarticular Infection. Approximately half of all bacterial osteoarticular infections occur in children younger than 5 years. (40) A population-based prospective study conducted in France in 2008 to 2009 reported the incidence of osteoarticular infections in children to be 7.1 in 100,000 children, with *S aureus* most commonly identified as the causative organism. (4)(41) Although MSSA remains a predominant cause of osteoarticular infections, the incidence of MRSA has been increasing (accounting for 0.8% in 1997 and increasing to 15.1% in 2012). (40)(42)

Initial empirical antibiotic treatment for osteoarticular infections should be administered IV. Empirical therapy for presumed or proven MSSA involvement should be nafcillin or oxacillin, although cefazolin may be used given that dosing is convenient at every 8 hours compared with every 6 hours for the semisynthetic penicillins. The empirical treatment for osteomyelitis and septic arthritis is vancomycin when CA-MRSA rates are greater than 10%. (2)(4) Alternatives include clindamycin (if clindamycin resistance is low and there is no associated bacteremia) and linezolid. (4)(21) The minimum treatment duration is 3 to 4 weeks for septic arthritis and 4 to 6 weeks for osteomyelitis, predicated on clinical response and normalization of inflammatory markers, particularly the erythrocyte sedimentation rate (ESR). (4)(21) The decision on final therapy, including drug and mode of delivery (IV versus oral), should include discussion on whether the pathogen has been identified, whether the treatment course was complicated by poor clinical or microbiologic response (such as prolonged secondary bacteremia), compliance of patient and family with possible oral regimen, and availability of medical facilities for families to seek care for unexpected complications. Early involvement of an orthopedic surgeon is important in both diagnosis and treatment of osteoarticular infections. (4)

Ocular Infections. *S aureus* has been identified as a causative organism in ocular infections. (43)(44) Ocular infections range from mild to severe, conjunctivitis to orbital cellulitis. A retrospective review of pediatric MRSA ocular infections in a northern California health-care system showed a 12.1% increase in MRSA causing ophthalmologic infections over a 5-year period (2000–2005). (45) Of all MRSA ocular infections, 40% manifested as conjunctivitis, with preseptal cellulitis (25%), orbital cellulitis

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(19%), dacryocystitis (11%), and eyebrow abscesses (3%) being reported (2% of reported MRSA ocular infections did not define the primary site). (45) Of note, organism identification is low, approximately 30% in some studies. (43)(44)

Empirical treatment for preseptal cellulitis should target *S aureus* and *S pyogenes*. (46)(47)(48) For postseptal cellulitis, antibiotic treatment should include activity against anaerobic and gram-positive organisms. (46) In a MRSA-prevalent community, vancomycin or clindamycin should be used for empirical treatment pending susceptibility results. (46) Parenteral antibiotics should be continued until the eye is clearly improving, at which point the patient can be transitioned to oral therapy to complete a 2-week duration. (46)

TOXIN-MEDIATED ILLNESS

Food Poisoning

S aureus food poisoning is due to the ingestion of preformed enterotoxins that are introduced into food by a person colonized or infected with *S aureus*. (1) There is rapid onset of illness—approximately 4 hours between ingestion and onset of symptoms. (1) Symptoms include nausea, vomiting, diarrhea, abdominal pain, and, in some patients, fever. (1)

Because this illness is due to ingestion of preformed toxin, antibiotics are unnecessary, and the patient needs supportive care only. (1)

Staphylococcal Scalded Skin Syndrome

Some strains of *S aureus* produce exfoliative toxins that are implicated in SSSS. (1) The toxins spread hematogenously and result in fever, erythema, and destruction of the proteins that are responsible for maintaining a crucial connection in the skin. (1) The toxin cleaves the desmoglein 1 glycoprotein in the stratum corneum, leading to bullae. These will rupture and result in denuded skin. Some of these patients have a positive Nikolsky sign. Staphylococcal scalded skin syndrome is a clinical diagnosis, but *S aureus* may be cultured from an affected site. (1)

Viable *S aureus* can continue to produce exfoliative toxins and propagate the disease. Antibiotics should be given for SSSS; this will not reverse the destruction of the skin but can prevent further damage. (1) The treatment of choice is an IV BLRBL or vancomycin if CA-MRSA prevalence is high. (2)(22) It may help to regard and manage patients with SSSS as if they possess severe partial-thickness burns, given possible high insensible losses due to capillary leak and damaged skin barrier.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is mediated by TSS toxin 1, or the combination of staphylococcal enterotoxin B and staphylococcal enterotoxin C toxins. The signs and symptoms include rapid onset of fever, a widespread rash resembling a sunburn (erythroderma), hypotension, and multisystem organ dysfunction. (1)(2) Risk factors for TSS include the presence of a strain able to produce the aforementioned toxin(s). The initial site of entry or infection may be unremarkable because TSS toxin 1 has the ability to dampen the local inflammatory response. (1) The mucous membranes (vagina, nasopharyngeal), wound (if present), and blood should be cultured as part of the diagnostic evaluation. (1) The main focus of treatment includes management of hypovolemic shock (given high insensible losses due to capillary leak), respiratory failure, and infection.

Intravenous antibiotics should be initiated empirically to treat *S aureus* and to inhibit protein synthesis to prevent further toxin from being produced. (1)(2) This antibiotic regimen includes an IV BLRBL and clindamycin (for disruption of protein synthesis, ie, toxin production), and often vancomycin given concern for MRSA. Once culture results are available, the antibiotics should be tailored to susceptibilities, and treatment duration is 10 to 14 days. (2) If there is a localized infection that is the inciting event, treatment should include adequate incision and drainage, and removal of a foreign body if present. (2)

ANTIMICROBIALS

The choice of antibiotic for infections suspected or confirmed to be secondary to *S aureus* depends on several factors. First is the severity of the presenting illness. Inadequate treatment may not be immediately detrimental for a patient presenting in the office with cellulitis but will have dire consequences in a patient with sepsis. Another factor is the rate of MRSA present in the community, which drives the use of vancomycin or other MRSA-active agents for empirical treatment. Bactericidal agents are always preferred over bacteriostatic antibiotics, although β-lactam allergies or the presence of MRSA may not always allow the use of bactericidal agents. Table 2 summarizes the following antibiotics.

For MSSA, nafcillin, oxacillin, and a first-generation cephalosporin (cefazolin) are first-line parenteral antibiotics. The mechanism of action of β-lactams (penicillins and cephalosporins) is inhibition of bacterial cell wall synthesis. β-Lactams bind to PBPs, which prevents a new disaccharide

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TABLE 2. **Antibiotics Used for *Staphylococcus aureus* in the Pediatric Population**

ANTIBIOTIC	MECHANISM OF ACTION	ADMINISTRATION	DOSING	MAXIMUM
Nafcillin	Inhibition of bacterial cell wall synthesis by binding of PBPs	IV	200 mg/kg per day divided every 6 h	2 g/dose, 12 g/d
Oxacillin	Inhibition of bacterial cell wall synthesis by binding of PBPs	IV	200 mg/kg per day divided every 6 h	2 g/dose, 12 g/d
Cefazolin	Inhibition of bacterial cell wall synthesis by binding of PBPs	IV	75–150 mg/kg per day divided every 8 h	6 g/d
Cephalexin	Inhibition of bacterial cell wall synthesis by binding of PBPs	PO	50–100 mg/k per day divided every 6–8 h	4 g/d
Vancomycin	Inhibition of bacterial cell wall synthesis by binding of D-alanyl-D-alanine	IV	15–20 mg/kg per dose every 6 h[a]	2 g/d
Clindamycin	Inhibition of bacterial protein synthesis by binding 50S ribosome to inhibit transpeptidation	IV or PO	40 mg/kg per day divided every 6–8 h	IV: 4.8 g/d PO: 1.8 g/d
Linezolid	Inhibition of bacterial protein synthesis by binding 50S ribosome to inhibit the initiation process	IV or PO	Age <12 y: 10 mg/kg per dose every 8 h Age ≥ 12 y: 600 mg every 12 h	600 mg/dose
Doxycycline	Inhibit bacterial protein synthesis by binding 30S ribosomal subunit preventing tRNA from binding	IV or PO	2.2 mg/kg per day divided every 12 h	200 mg/d
TMP-SMX	Inhibition of bacterial DNA synthesis by blockage of metabolic pathways	IV or PO	6–12 mg TMP/kg per day divided every 12 h	160 mg TMP/dose

IV=intravenous, PBP=penicillin-binding protein, PO=oral, TMP-SMX=trimethoprim-sulfamethoxazole.

[a] *Vancomycin dosing and goal trough level depend on the age of the patient, severity of infection, and renal insufficiency.*

from joining the peptidoglycan polymer, therefore blocking the formation of the peptidoglycan layer that surrounds the bacterium. The BLRBLs are bactericidal against *S aureus* and are superior to vancomycin, which has a slow kill time against *S aureus,* making it, in effect, bacteriostatic. (21) Adverse effects of BLRBLs include bone marrow suppression and interstitial nephritis. Overall, a BLRBL should be used for MSSA infections. Oral conversion to cephalexin is possible when using these empirical agents.

For MRSA, vancomycin is usually the first consideration in patients with serious infections, including bacteremia and endovascular infections. Vancomycin is a glycopeptide that inhibits the synthesis of the bacterial cell wall. Vancomycin binds to a subunit of the peptide side chain (D-alanyl-D-alanine). Owing to its large molecular size, vancomycin occupies a sizable area and, thus, prevents further synthesis of the peptidoglycan polymer around the bacterium. For clinical use, vancomycin is often considered bacteriostatic. Although the minimum bactericidal concentration is similar to the MIC of vancomycin against *S aureus*, the rate of *S aureus* killing is slower for vancomycin compared with other antistaphylococcal antibiotics. (49) Dosing of vancomycin is based on the age of the patient, severity of infection, and known or developing renal insufficiency. Therapeutic drug monitoring is usually conducted with serum trough levels (obtained by venipuncture 1 hour before dose). For invasive and severe infections, the goal trough level for vancomycin is 15 to 20 μg/mL. (21) When the practitioner is empirically using vancomycin, de-escalation to an oral agent may be difficult if bacterial cultures were not obtained before initiation of therapy or remain sterile.

Other antibiotics used for MRSA as well as MSSA infections (usually with less severe clinical presentations) include clindamycin, linezolid, doxycycline, and TMP-SMX.

Clindamycin is an attractive option for practitioners who want to use an agent with generally effective treatment of MSSA and MRSA. The mechanism of action of clindamycin is inhibition of protein synthesis by binding the 50S ribosomal subunit preventing transpeptidation. Advantages of clindamycin include excellent tissue penetration (bone, abscess) and the high bioavailability of the oral drug. However, clindamycin is a bacteriostatic drug against *S aureus* and may not have activity against all isolates of MSSA or MRSA. These 2 reasons should be recalled if the

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provider is facing a patient with poor clinical response while taking empirical clindamycin. Furthermore, clindamycin has poor penetration into cerebrospinal fluid and should not be used in primary bacteremia because it does not have this Food and Drug Administration (FDA) indication. (21) The most common adverse effect of clindamycin is diarrhea. (21)(50) The practitioner should balance the benefits and risks of using clindamycin when confronted with a suspected *S aureus* infection.

Linezolid is often used in the ambulatory setting as an oral alternative to IV vancomycin, particularly for SSSI and pneumonia. (21) The mechanism of action is inhibition of protein synthesis by binding the bacterial 50S ribosomal subunit, which prevents the assembly of the entire initiation complex. Linezolid is bacteriostatic against *S aureus*. (50) Bioavailability is almost 100%. (50) Adverse effects include reversible bone marrow suppression (thrombocytopenia, neutropenia, and/or anemia), irreversible neuropathy, gastrointestinal upset, lactic acidosis, and hyperglycemia. (21)(50) The benefit of linezolid is ease of transition between parenteral to oral administration and its effectiveness against MRSA.

Doxycycline is an excellent choice for outpatient treatment for SSSI and is active against MRSA. Doxycycline is a tetracycline that is bacteriostatic at lower concentrations and bactericidal at higher concentrations. (21)(50) The mechanism of action is inhibiting protein synthesis by binding the 30S ribosomal subunit preventing transfer RNA from binding. Adverse effects include gastrointestinal upset (nausea and vomiting) and phototoxicity. (50) It is prudent to avoid prolonged courses (>21 days) in young children given concern for discoloration of developing tooth enamel.

Outpatient treatment with TMP-SMX is an attractive option for MRSA. (21) It is bacteriostatic. The mechanism of action is a blockage of metabolic pathways that are essential for bacterial DNA synthesis and, therefore, growth. The sulfonamide component can displace bilirubin from albumin. This displacement increases the serum level of unconjugated bilirubin and elevates the risk of bilirubin-induced neurologic dysfunction. (21) Although FDA labeling cautions against use in infants younger than 2 months, it may be used safely in full-term infants as early as 2 weeks after birth as physiologic jaundice is resolving. (1) For those with renal disease there is an increased risk of hyperkalemia from use of this medication. (21) Often, TMP-SMX is used in the outpatient setting, but the practitioner should bear in mind that it has poor activity against *S pyogenes*, often in the differential diagnosis for SSSIs.

DECOLONIZATION

The goal of decolonization is the reduction of the infectious burden of a particular organism from a specific body site. In the general population, 20% have persistent colonization with *S aureus*, 60% are intermittently colonized, and 20% are never colonized. (1) Decolonization of patients with persistent or intermittent colonization may be desirable in situations involving recurrent SSSIs, atopic dermatitis, or those anticipating surgeries with implantable or prosthetic materials (such as prosthetic joints).

A decolonization program should include considering the body area of interest, the medication, the duration of the program, and the number of household members needed to treat to reduce transmission. The most common area of *S aureus* colonization is the anterior nares. (1) Many decolonization regimens use mupirocin and anerdian in the anterior nares. (51) Mupirocin is prepared as a 2% antibiotic ointment with activity against several gram-positive and gram-negative organisms. (51) Anerdian is a compound containing ethanol, iodine, and chlorhexidine. (51) Targeting the entire body surface area with washes such as chlorhexidine for a duration of 5 days, or bleach baths (ratio is one-quarter to one-half cup of bleach in a full bath) administered 2 to 3 times a week, have been used with varying effects on colonization. (2) The most effective regimen (body area, medication, duration) has not been found.

There is no evidence that decolonization has sustained effects. (51) A Cochrane review regarding decolonization found 188 articles regarding effectiveness of *S aureus* decolonization. Only 2 studies were deemed eligible for analysis, and both were inconclusive: 1) mupirocin versus placebo and 2) anerdian versus no treatment. (51)(52)(53) Another publication that reviewed 19 articles suggested a reduction in surgical site infections after decolonization. (9) These decolonization regimens varied and included mupirocin alone, or mupirocin with either chlorhexidine or triclosan. (9) Not all the studies had statistically significant reductions in surgical site infections. (9)

Despite the lack of evidential support, decolonization can be considered in certain circumstances, as described previously herein. For patients with atopic dermatitis or recurrent SSSI, decolonization can be considered if recurrence persists despite excellent hand hygiene and wound care. (11) Decolonization may not work, as evidenced by 1 study showing that 20% of patients displayed persistent colonization. (54) If decolonization is successful, risk of recurrence is high: up to 70% of decolonized patients experience recurrence of SSSI within 1 year. (11)

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Outside of surgical site infection prevention, most decolonization regimens include household members. As noted previously, household exposures (ie, close contacts) may play a role in colonization. (54) Therefore, decolonization of household contacts may alter the colonization pattern in the index case, which could result in a successful and sustained reduction of SSSIs. (54)

Summary

- Based on observational and epidemiologic studies, approximately one-third of the population is colonized with *Staphylococcus aureus,* and colonization of the individual and/or household members is a risk factor for *S aureus* infection.
- From evidence-based guidelines, empirical treatment for non–life-threatening infections suspected to be from *S aureus* should include methicillin-sensitive *S aureus* (MSSA) treatment, ideally a β-lactamase–resistant β-lactam (BLRBL). Methicillin-resistant *S aureus* (MRSA) treatment may be included (either with a second drug or more often as clindamycin monotherapy) in geographic areas with high rates of community-acquired MRSA.
- From published clinical guidelines and expert opinion, empirical treatment for life-threatening and invasive *S aureus* infections should cover both MSSA and MRSA. This includes a parenteral BLRBL (for MSSA) and vancomycin (for MRSA) while awaiting culture results and susceptibilities.
- From evidence-based guidelines, the treatment of staphylococcal scalded skin syndrome includes parenteral antibiotics and fluid and electrolyte management.
- Evidence-based guidelines recommend that the treatment of toxic shock syndrome due to *S aureus* includes drainage of the nidus of infection, antibiotics targeted to inhibiting bacterial cell wall synthesis (such as nafcillin/oxacillin or vancomycin), and inhibiting protein synthesis (such as clindamycin).
- On the basis of Cochrane review and expert opinion, decolonization practices have little evidential support. These practices may be used if the patient experiences recurrent skin and skin structure infections despite optimization of hand hygiene and wound care. If decolonization is recommended, all members in the household should also undergo this process.

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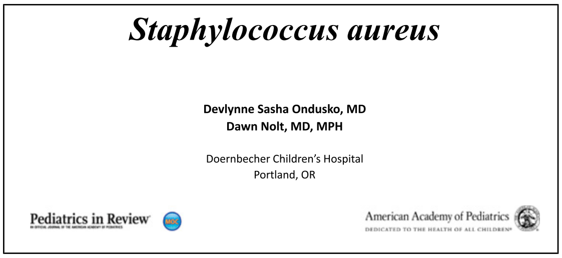

Staphylococcus aureus

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Pediatrics in Review
American Academy of Pediatrics
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PIR Quiz

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1. A previously healthy 3-year-old boy is brought to the office due to a painful lesion on his right thigh. He has not had fever and is eating well. Mom states that the area started to have whitish drainage this morning. His father has a history of recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections. There is a 3-cm erythematous area of his right thigh that has purulent drainage. A culture is obtained that grows MRSA. Which of the following is the mechanism of resistance to methicillin and other β-lactam antibiotics?

   A. Alteration of penicillin-binding protein.
   B. β-Lactamase production.
   C. Decreased antibiotic membrane permeability.
   D. Efflux mechanism.
   E. Modification of the ribosomal antibiotic target.

2. A previously healthy 9-month-old girl is admitted to the hospital due to cellulitis of her left buttock that is not improved after 2 days of treatment with cephalexin. She is fussy but consolable. Her temperature is 102.4°F (39.1°C). There is a 12×15-cm tender area of erythema and induration of her right buttock with central fluctuance. Incision and drainage is performed and sent for culture. The hospital antibiogram notes that 36% of *S aureus* isolates were resistant to clindamycin. Which of the following is the most appropriate initial antibiotic treatment regimen?

   A. Ampicillin-sulbactam.
   B. Ceftriaxone.
   C. Nafcillin.
   D. Trimethoprim-sulfamethoxazole (TMP-SMX).
   E. Vancomycin.

3. A 20-month-old boy is admitted to the hospital due to a 3-day history of fever. He started limping 4 days ago and now will not bear weight on his left leg. He has also developed swelling around his left knee. A magnetic resonance image of the left leg bone shows marrow edema of the left distal femur and a subperiosteal fluid collection. The latest antibiogram released by the hospital lists a 26% incidence of MRSA isolated from the community. A blood culture is obtained, and he is started on intravenous (IV) vancomycin and ceftriaxone. He is taken to the operating room for incision and drainage. The blood culture and subperiosteal abscess culture grow *S aureus* susceptible to oxacillin (methicillin susceptible), vancomycin, linezolid, tetracycline, and TMP-SMX. He has no known drug allergies. Transition to which of the following IV antibiotics is most appropriate?

   A. Ampicillin.
   B. Doxycyline.
   C. Linezolid.
   D. Nafcillin.
   E. TMP-SMX.

4. By day 7 of hospitalization the same 20-month-old boy as in question 3 is significantly improved. He has been afebrile for 48 hours and is starting to bear weight on his left leg. A repeated blood culture has no growth after 72 hours. He is discharged on oral cephalexin.

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Which is the most appropriate total duration of antimicrobial therapy if he continues to clinically improve with normalization of his ESR?

- A. Fourteen days.
- B. Six weeks.
- C. Ten days.
- D. Twelve weeks.
- E. Twenty-one days.

5. A 14-year-old girl with a history of recurrent acute sinusitis is admitted to the PICU after presenting to the emergency department with a 2-day history of fever and diffuse myalgia. Her most recent menstrual period ended 6 days ago. Over the past day she has had 2 episodes of vomiting and 5 watery stools. She has also developed a rash. In the emergency department her temperature was 102.2°F (39°C), heart rate was 112 beats/min, respiratory rate was 28 breaths/min, blood pressure was 96/60 mm Hg, and oxygen saturation was 97%. She was given 2 boluses of IV normal saline and is currently receiving a third bolus. She also received IV vancomycin and IV ceftriaxone. Her blood pressure, after 2 fluid boluses, currently is 111/70 mm Hg, and her heart rate is 84 beats/min. She is tired appearing but can answer questions appropriately. She has conjunctival injection and a diffuse macular erythroderma. Her capillary refill time is 2 seconds. The remainder of her examination findings are normal. Laboratory tests show a white blood cell count of 15,200/μL (15.2×10^9/L), hemoglobin level of 12.4 g/dL (124 g/L), platelet count of $85 \times 10^3/\mu$L (85×10^9/L), aspartate aminotransferase level of 106 U/L (1.8 μkat/L), creatine phosphokinase level of 232 U/L (3.9 μkat/L), blood urea nitrogen level of 15 mg/dL (5.4 mmol/L), and creatinine level of 0.8 mg/dL (70.7 μmol/L). Blood culture is pending. Which of the following is the most appropriate next step in management?

   - A. Computed tomographic scan of the abdomen and pelvis.
   - B. Fresh frozen plasma transfusion.
   - C. IV clindamycin.
   - D. IV doxycycline.
   - E. IV phenylephrine.

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Staphylococcus aureus

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health maintenance, acute care, and emergency department visits. This would help highlight and perhaps reinforce in the consciousness of adolescents the importance of this issue. Parents serve as role models, and because adolescents will often emulate their parents' behaviors, addressing this issue to parents is also needed. Although studies show that adolescents recognize the dangers with TWD, they still report participating in the behavior. As with other injury prevention strategies, it seems that a focus on why abstaining from TWD is beneficial is a more powerful approach than the focus on harm. For some adolescents, compulsive texting may be a behavioral addiction and may need to be addressed. Other innovative strategies that need further evaluation include peer to peer education, school-based interventions, messages on social media, and capabilities to directly observe behaviors while driving.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

CME Quiz Clarification

An astute reader noted a need for clarification in the CME quiz for the May 2017 review "Screening for Poverty and Poverty-Related Social Determinants of Health" (Berman RS, Patel MR, Belamarich PF, Gross RS. *Pediatric Rev.* 2018; 39(5):235-246, DOI: 10.1542/pir.2017-0123). The child featured in the question 5 stem has been changed from a 1-year-old-boy to a 7-year-old boy to more closely coincide with the answer options presented. The online version of the quiz has been updated, and a clarification notice has been posted with the online version of the article. The journal appreciates the clarification.

CME Quiz Correction

An error appeared in the print version of the CME quiz for the June 2018 review "*Staphylococcus aureus*" (Ondusko DS, Nolt D. *Pediatr Rev.* 2018;39(6):287-298, DOI: 10.1542/pir.2017-0224). In question 5, the platelet count should read "85 x $10^3$$\mu$L (85 x 10^9/L) …" The online version of the quiz is correct, and a correction notice has been posted with the online version of the article. The journal regrets the error.

Pediatrics in Review
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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An erratum has been published regarding this article. Please see the attached page for:
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Intellectual Disabilities

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Education Gaps

1. Pediatricians must have knowledge of the diagnostic criteria and levels of severity of intellectual disability (ID).
2. Pediatricians should be informed about current developments in the evaluation of a child with ID.
3. Pediatricians must be familiar with treatment and resources for children with ID.

Objectives

After completing this article, readers should be able to:

1. Formulate a plan for the evaluation of children with intellectual disability (ID) both in terms of coming to a diagnosis (evaluation of cognitive and adaptive skills) and performing a diagnostic evaluation.
2. Formulate treatment options and referral for services for children with ID.

AUTHOR DISCLOSURE Dr Purugganan has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAIDD	American Association of Intellectual and Developmental Disabilities
AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
CT	computed tomographic
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
GDD	global developmental delay
ID	intellectual disability
IEP	Individualized Education Program
MRI	magnetic resonance imaging
WISC-V	Wechsler Intelligence Scale in Children-V
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence-IV

Intellectual disability (ID) is a neurodevelopmental disorder that is characterized by deficits in both intellectual functioning and adaptive functioning, whose onset is in the developmental period. (1) It affects approximately 1% to 3% of the population. (2) *Intellectual disability* has replaced the former term, *mental retardation,* through a federal statute (Rosa's Law, Public Law 111-256). *Global developmental delay (GDD)* is the term used to describe children aged 0 to 5 years with significant delays in 2 or more areas of development. (1) Although these delays may be transient, it is estimated that approximately two-thirds of children diagnosed as having GDD would eventually carry the diagnosis of ID after 5 years of age. (3)

As part of routine health-care visits, the American Academy of Pediatrics (AAP) recommends developmental surveillance at every well-child visit and formal developmental screening at ages 9, 18, and 24 or 30 months. (4) Screening instruments such as the Ages and Stages Questionnaire, the Pediatric Evaluation of Developmental Skills, and the Denver Developmental Screening Test-II help to identify children who will require more formal developmental assessments, where a child's developmental skills are more thoroughly evaluated and that will likely include testing of cognitive abilities.

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PRESENTATION

Intellectual disability may present in various ways and at different ages in the pediatric patient. The more severe the impairment, the more likely ID is to present and be diagnosed earlier. Correspondingly, the milder the impairment, the more likely it is to manifest at an older age. It is possible that milder forms of ID may go unrecognized until the school-age years. A child with ID may present initially with receptive and expressive language delays, adaptive skills delays (eg, toileting, dressing), fine motor deficits, difficulties in problem-solving skills, social immaturity, and behavioral difficulties. It is important to consider that intelligence/developmental tests during the first 3 years of life involve many sensorimotor tasks that may affect the accurate measurement of the cognitive level of a child with a motor problem (eg, cerebral palsy, hypotonia) or sensory impairment (visual and auditory). Among the different areas of development monitored in early childhood (language, problem-solving, gross/fine motor, personal-social skills), gross motor skills are the least correlated with ID.

ASSESSMENT

Assessment of Intellectual Functioning

Intellectual functioning is measured by standardized instruments such as the Wechsler Intelligence Scale in Children-V (WISC-V), the Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV), and the Stanford-Binet Intelligence Scales-V. These are generally performed by a certified psychologist or special educator. These instruments are designed to measure a child's general intellectual ability and include verbal and nonverbal subtests. Persons with ID exhibit deficits in both verbal and nonverbal domains, although not necessarily to the same degree. An overall full-scale IQ score is derived from the combination of verbal and nonverbal IQ scores.

The WISC-V and WPPSI-IV include the following indices: verbal comprehension index, visuospatial index, fluid reasoning, working memory, and processing speed. The Stanford-Binet subtests include knowledge, quantitative reasoning, visuospatial reasoning, working memory, and fluid reasoning. These instruments can be administered in children as early as approximately age 2 years (Stanford Binet-V) to 2½ years (WPPSI-IV), although it is important to note that intelligence scores become more stable after 5 years of age. (5)(6)(7) People with intelligence scores more than 2 SD below the mean are considered to fall in the ID range. Using the normal curve to delineate levels of intelligence with a mean IQ score of 100 and a standard deviation of 15, it is estimated that approximately 2.5% of the population would fall in the ID range with IQ scores less than 70 (2 SD below the mean). Those with IQ scores of 70 to 84 are considered to have borderline intelligence. In school, children with borderline intelligence may be considered "slow learners" but not to the same degree as children with ID. Making a diagnosis of ID is not always straightforward; it may require a few visits to fully assess a child, and ongoing follow-up may be necessary.

Assessment of Adaptive Functioning

Adaptive functioning is measured through questionnaires such as the Vineland Adaptive Behavior Scales and the Adaptive Behavior Assessment System, (5) which are administered by certified clinicians such as psychologists or social workers with information obtained from the patient's primary caregivers. In the *Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition,* adaptive functioning is operationalized in terms of 3 domains: the conceptual domain (eg, competence in memory, language, academics, judgment), the social domain (eg, social awareness, interpersonal communication skills, friendships), and the practical domain (eg, learning and self-management). Impairment in at least 1 of these domains, wherein ongoing support is needed, should be present to meet the definition of ID. (1)

The American Association of Intellectual and Developmental Disabilities (AAIDD), the oldest interdisciplinary professional organization that has been instrumental in the definition and recognition of ID and its earlier iterations, uses a similar definition of ID as the *DSM-V*. The AAIDD defines ID as a disability characterized by "significant limitations in both intellectual functioning and adaptive behavior" with the onset of deficits before 18 years of age. (8)

LEVELS OF SEVERITY

The *DSM-V* and the AAIDD characterize the severity of ID based on a person's adaptive functioning and the amount of support a person needs. These are described and summarized in the following subsections (Table 1). (1)(6)

Mild ID

A person with mild ID may manifest difficulties in late preschool or the early school-age years. They may have difficulties in the academic setting (early reading, writing, arithmetic, time, and money) and seem more socially immature compared with other children their age. Communication and thinking may be more concrete and less mature than that of their peers. Although they may function

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TABLE 1. **Levels of Severity of Intellectual Disability (ID)**

LEVEL OF ID (% CHILDREN WITH ID)	LEVEL OF SUPPORT (IN CONCEPTUAL, SOCIAL, PRACTICAL DOMAINS)	ASSOCIATED ESTIMATED IQ SCORE	PROJECTED ULTIMATE ACADEMIC ACHIEVEMENT
Mild (85%)	Intermittent	55–70	Up to sixth-grade level
Moderate (10%)	Limited	40–55	Up to second-grade level
Severe (3%–4%)	Extensive	25–40	Preschool level
Profound (1%–2%)	Pervasive	<25	–

Note: The level of severity is based on the level of adaptive functioning and support. (1)(6)

appropriately in matters of personal care and many even eventually live independently, they may need support intermittently, particularly in complex daily living situations. Some may be able to reach a sixth-grade level in academic functioning.

Moderate ID

A person with moderate ID generally presents earlier than those with mild ID, manifesting with learning and language difficulties in the preschool years and deficits in social and communication behavior, which require limited although possibly substantial support. Those affected may ultimately be able to perform basic tasks for personal care (eg, dress, toilet, and eat independently), but significant amounts of support time and teaching may be needed. During adulthood, they may be employed in jobs that require minimal communication and cognitive skills and may be able to participate in all household tasks but with ongoing support and teaching. Some may be able to reach a second-grade level in academic functioning.

Severe ID

A person with severe ID has limited capacity to understand written language and the concepts of numbers and time and would need extensive support from caretakers throughout life. Spoken language is also very limited, and they may have limited understanding of speech/language and gestural communication. Children with severe ID would require extensive support and supervision for all activities of daily living. Some may reach the pre-K level in academic functioning.

Profound ID

A person with profound ID has conceptual skills that do not go beyond the concrete, and ability mainly involves manipulation of objects, at best. They have very limited understanding of symbolic language, although they may be able to understand basic instructions. A person with profound ID requires pervasive support and is dependent in all aspects of personal care and daily living.

In the *DSM-IV* and *DSM-IV-TR*, the previous editions of the *DSM*, (9) levels of ID were extrapolated by increasing standard deviations from the mean IQ; thus, mild ID was defined as IQ scores between 2 and 3 SD below the mean of 100 (IQ scores from 50–55 to approximately 70); moderate ID corresponded to IQ scores between 3 and 4 SD below 100 (IQ scores from 35–40 to 50–55); severe ID was defined as IQ scores between 20 to 25 and 35 to 40; and profound ID corresponded to IQ scores less than 20 to 25. Although this classification may still be useful, using IQ scores solely does not accurately and completely reflect how well an individual is able to function, hence the shift in the classification of the levels of ID based on the individual's level of adaptive function.

ETIOLOGY

There are many different etiologies for ID: genetic disorders (eg, chromosomal disorders, including X chromosome disorders, contiguous gene deletions, and single-gene disorders), environmental causes (eg, alcohol and other teratogens, prenatal infections), traumatic brain injury, neurologic/brain disorders, nutritional deficiencies, and inborn errors of metabolism. A significant number of people with ID have no identifiable cause (Table 2). It is more likely to identify a biological cause in more significant forms of ID (such as moderate, severe, and profound ID) than in mild ID, which may be influenced by cultural, linguistic, and societal difficulties. (5)

Genetic Causes of ID

Online Mendelian Inheritance in Man (10) lists approximately 800 genetic syndromes associated with ID. These syndromes may have X-linked, autosomal dominant, or

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TABLE 2. Causes of Intellectual Disability

Genetic syndromes
Chromosomal disorders, eg, Down syndrome
Contiguous gene deletions, eg, Williams syndrome, Angelman syndrome
Single-gene deletions, eg, fragile X syndrome, Rett syndrome
Environmental causes
Alcohol and other teratogens
Prenatal infections
Early childhood central nervous system infections
Traumatic brain injury
Central nervous system disorders/malformations
Inborn errors of metabolism
Nutritional (eg, severe malnutrition, chronic iron deficiency)
Not known

autosomal recessive inheritance. Medical evaluation for those with syndromic forms of ID will be based on known clinical manifestations of the genetic syndrome. (10)(11)(12) Table 3 summarizes some of the more common genetic syndromes associated with ID.

Down syndrome is the most common genetic cause of ID, with prevalence of 1 in 800, with 95% of cases due to trisomy 21, 4% to 5% due to an unbalanced translocation between chromosome 21 and another chromosome (usually chromosome 14), and 1% attributed to mosaicism. The clinical phenotype is very well-known and includes a distinct facies, congenital heart disease, hypothyroidism, gastrointestinal disorders, and hypotonia. Intelligence is usually in the mild-moderate range of ID, with verbal skills weaker than nonverbal skills. It is also associated with early Alzheimer disease and depression. The AAP has published health maintenance guidelines for children with Down syndrome. (13)

Fragile X syndrome is a trinucleotide repeat disorder (CGG) and is the most common inherited cause of ID, affecting 1 in 4,000 individuals. Although it is much more common in males, fragile X syndrome may be diagnosed in girls as well. Fully affected males (with triplet repeats >200) manifest with significant ID as well as clinical features that may include relative macrocephaly, an elongated face, prominent ears, hyperextensible joints, and large testes in postpubertal individuals. Females with fragile X syndrome may present with milder forms of cognitive impairment. Fragile X syndrome also has a well-recognized association with autism spectrum disorders. (2)

Rett syndrome is due to a mutation of the *MECP2* gene found in the X chromosome. It is primarily seen in girls (although it has also been identified in boys), where the clinical presentation includes a deceleration in the rate of head growth during the second year of life, hand-wringing and handwashing movements, language deficits/regression, and ID. It is more likely that males with *MECP2* mutations present with neonatal encephalopathy than with GDD/ID. (2)

Certain contiguous gene disorders are also associated with ID. (10)(11)(12) Williams syndrome is caused by a deletion in chromosome 7q11 and presents with elfinlike facial features, mild to moderate ID (with nonverbal function being a significant weakness), and cardiac and renal manifestations. Angelman and Prader-Willi syndromes are a result of genetic imprinting, where clinical manifestations depend on which parent contributes to the deletion in chromosome 15q11.2-q13. Less commonly, these syndromes can also be attributed to uniparental disomy (2 copies of a chromosome from the same parent). Angelman syndrome is due to a maternally derived deletion (or paternal disomy) and is associated with severe-profound ID, microcephaly, prognathism, and abnormal hand movements, whereas Prader-Willi syndrome is caused by a deletion in the paternally derived chromosome (or maternal disomy). The clinical course of patients with Prader-Willi syndrome is unique and consists of hypotonia and feeding difficulties in the neonatal period and obesity, atypical facial features, some degree of ID (low average to moderate ID), and psychiatric conditions (eg, obsessive compulsive disorder, skin picking) starting in toddlerhood or the preschool years. Smith-Magenis syndrome is caused by a deletion in the short arm of chromosome 17 (17p11.2) and is characterized by facial features such as midface hypoplasia and a broad nasal bridge, short stature, medical conditions such as visual problems, peripheral neuropathy, mild-moderate ID, sleep disturbances, and stereotypic and self-injurious behaviors. Miller-Dieker syndrome is due to a deletion in chromosome 17 and is associated with significant ID, microcephaly, and lissencephaly, where the brain is small and smooth due to a paucity of gyri and sulci.

Single-gene deletions associated with ID, aside from fragile X syndrome and Rett syndrome, include Rubinstein-Taybi syndrome (ID, short stature, microcephaly, abnormalities of the thumbs and toes) and tuberous sclerosis (skin manifestations, ID, autism, seizures, particularly infantile spasms). (10)(11)(12)

Environmental Causes of ID

Environmental causes of ID may also present with a set of symptoms that compose a syndrome. Fetal alcohol spectrum disorder results from prenatal exposure to alcohol and

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TABLE 3. **Common Genetic Syndromes Associated with Intellectual Disability (ID)**

SYNDROME	GENETIC ABNORMALITY	DEVELOPMENTAL PROFILE	COMMON PHYSICAL FINDINGS
Down	Trisomy 21 (95%) Translocation (4%) Mosaicism (1%)	Mild to moderate ID (Verbal - low) Hypotonia Early Alzheimer disease	Down facies Congenital heart disease Hypothyroidism Gastrointestinal abnormalities
Fragile X	CGG trinucleotide repeat (>200)	ID (typically moderate) Learning disorders Autism spectrum disorder	Elongated face Macrocephaly Prominent ears Hyperextensible joints Enlarged testes (postpuberty)
Rett	*MECP2* deletion	ID Stereotypic hand mannerisms Language regression	Deceleration in head growth Gait abnormalities
Williams	7q11 deletion	Mild to moderate ID (nonverbal - low)	Elfinlike facial features Cardiac (eg, supravalvular aortic stenosis) Renal abnormalities Hypertension
Angelman	Maternally derived deletion 15q (or paternal disomy)	Severe to profound ID Atypical hand mannerisms	Microcephaly Prognathism
Prader-Willi	Paternally derived deletion 15q (or maternal disomy)	ID (variable levels) Psychiatric conditions	Neonate: hypotonia/feeding difficulties Toddler: obesity, excessive appetite

is characterized by alcohol-related birth defects, microcephaly and growth retardation, facial features such as short palpebral fissures, thin upper lip, smooth philtrum, neurocognitive problems such as ID and ADHD, and behavioral difficulties. (14) Intrauterine infections (TORCH) may present with developmental disabilities, growth defects, retinopathy, intracranial calcifications, and abnormalities in head size such as microcephaly (eg, cytomegalovirus) or macrocephaly (eg, toxoplasmosis associated with hydrocephalus). Most recently, congenital Zika infection has been implicated in causing significant microcephaly and other brain abnormalities in infants, which may likely lead to ID. (15)

Significant hypoxic-ischemic injury in the neonate may present early on with significant GDDs, motor impairment such as muscle hypertonicity/spasticity, microcephaly or poor head growth, and seizures. Many children with severe hypoxic-ischemic encephalopathy will eventually be diagnosed as having ID as well as cerebral palsy. Prematurity, especially for children with younger gestational age and more complicated courses, also places a child at risk for intellectual impairment and developmental disorders. (16)

In the United States, there has been a significant decrease in the levels of environmental lead due to successful public health efforts implemented during the past few decades. Consequently, there has been a dramatic decrease in blood lead levels in children. Mildly elevated lead levels are still detected, and these have been shown to be associated with mild cognitive delays. Lead toxicity has been associated with a decline of 1 to 2 IQ points (measured at 5 years or older) for every 10-point increase in lead level (17)(18) and a decrease of more than 7 IQ points for the first 10 μg/dL. (19) The AAP recommends further research to look more closely into these associations, through studies where confounders such as socioeconomic factors are better controlled for. (17)

Through newborn screening, conditions that may have led to ID if left untreated are being identified. These conditions include phenylketonuria and congenital hypothyroidism. In 2006, the American College of Medical Genetics Newborn Screening Expert Group recommended that 29 treatable conditions be universally screened in the newborn. (20) There are variations in each state as to the complete set of disorders that are being tested for. Pediatricians should be familiar with the conditions that are tested for in their state and ensure that each newborn undergoes the state's newborn screening. The AAP has provided recommendations for pediatricians and medical homes as newborn screening has expanded. (21)

APPROACH TO EVALUATION

The approach to the evaluation for the etiology of the ID includes a thorough history, focused physical and neurologic

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examinations, and appropriate laboratory testing as warranted. (2)(7) History and physical examination together can identify the etiology in approximately 17% to 34% of cases of developmental delay. (7) Based on the history and physical examination findings, initial evaluation, including laboratory testing, genetic testing, and imaging, is determined.

History

The medical history includes a child's current developmental functioning and a chronology of attainment of developmental milestones, a history of educational interventions, and a detailed prenatal/perinatal/neonatal history, which should include any history of maternal medical conditions and outcomes of previous pregnancies, maternal infections, medication intake and substance use/abuse, and a review of the newborn metabolic and hearing screens. A 3-generation family history of developmental problems; ID; learning deficits; neurologic, metabolic, or genetic conditions; and consanguinity should be explored. The child's medical history should include any previous head injuries, central nervous system infections (such as meningitis or encephalitis), seizures and other neurologic conditions, and regression in skills.

Physical and Neurologic Examination

The physical examination focuses on growth parameters (especially head circumference), a thorough skin examination looking for lesions that may signify a neurocutaneous syndrome, a full neurologic examination, and evaluation for dysmorphic features that may suggest a genetic syndrome.

Evaluation of Head Size. Microcephaly, or a head circumference less than the third percentile for age, is highly associated with ID and is a manifestation of many disorders. Macrocephaly or a head circumference greater than the 97th percentile for age is associated with ID in the setting of certain genetic syndromes, such as fragile X syndrome and Sotos syndrome, as well as in patients with hydrocephalus. Autism spectrum disorder has also been associated with an enlarged head, especially in the first 5 years of life, (22) and in some of these cases, ID may be present.

Examination of the Skin. Neurocutaneous syndromes may also be associated with ID. (10)(11) Tuberous sclerosis is associated with skin findings such as ash leaf spots (hypopigmented macules), shagreen patches ("peau d' orange"–textured skin lesions), and facial angiofibromas. Neurofibromatosis, which is associated with attention-deficit/hyperactivity disorder, learning disorders, and, less commonly, ID, is characterized by café au lait spots, inguinal and axillary freckling, Lisch nodules on eye examinations, and neurofibromas in the body.

Dysmorphic Features. The clinician should take note of dysmorphic features and atypical features that may be manifestations of certain genetic syndromes as described previously.

LABORATORY EVALUATION

Evaluation of Syndromic Forms of ID

If the clinician suspects a specific syndrome as an etiology for the ID/GDD, laboratory tests to confirm or rule out this syndrome should be performed. This may include chromosome analysis for Down syndrome and fluorescence in situ hybridization testing when specific genetic disorders are suspected, such as Prader-Willi/Angelman syndrome, Smith-Magenis syndrome, Williams syndrome, 22q11 deletion, Miller-Dieker syndrome, cri du chat syndrome, and Wolf-Hirschhorn syndrome.

For patients with suspected TORCH and Zika infections, serologic testing, neuroimaging, eye examination, and hearing tests are recommended. (23) A referral to a genetics specialist may be considered for further evaluation of dysmorphic features.

Evaluation of Nonsyndromic ID of Unknown Etiology

The American Academy of Neurology has released reports with recommendations for the evaluation of nonsyndromic GDD/ID of unknown etiology. (7)(24) It is widely regarded among clinical geneticists that chromosomal microarray analysis, with a yield of approximately 15% to 20%, (25) should be the first-line cytogenetic test for these cases. There has been less universal consensus for fragile X testing, but many experts recommend fragile X testing in boys and girls with ID who have clinical features of fragile X syndrome (macrocephaly, prominent ears, hyperextensible joints, perseverative speech, enlarged testes in pubertal boys), as well as unexplained GDD/ID (in both sexes) if there is a family history of ID. Many geneticists also recommend fragile X testing for unexplained ID if the microarray result is normal. Karyotyping is recommended if there is a suspicion of aneuploidy (presence of an abnormal number of chromosomes in a cell) such as Down syndrome, a history of many miscarriages, or a family history of chromosomal abnormalities. Some clinicians recommend all 3—chromosomal microarray analysis, fragile X testing, and karyotyping—as the first-line evaluation for both boys and girls with nonsyndromic ID of unknown etiology considering the yield of approximately 2% for fragile X testing and 4% for karyotyping for these cases. (24) Microarray analysis does not detect balanced translocations (which a karyotype is able to), point mutations, or low level of mosaicism. (25) If microarray

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analysis reveals an abnormality, further genetic testing of the parents may be recommended. For females with severe to profound ID, testing for Rett syndrome (*MECP2* gene) is recommended. (24)(25)

Consultation and collaboration with a clinical geneticist may be very useful in the evaluation of children with ID, especially those with unexplained ID, syndromic ID, or more severe levels of ID. Clinical geneticists and genetic counselors may also be helpful in the interpretation of the results of genetic testing. (25) A newer form of genetic testing, whole exome sequencing, may be able to identify a genetic cause in up to 40% of patients with unexplained ID; however, it is not widely available at this time, and the implications of using whole exome sequencing in the routine evaluation of all children with ID, wherein other genetic abnormalities not related to ID may be unearthed, is still not fully understood and must be explored further. (2)(25)

Inborn errors of metabolism account for a small percentage (approximately 0%–5%) of children with unexplained ID. (2)(7)(26) Testing for these conditions has been recommended for cases that are clinically suggestive of a metabolic disorder. Most of these conditions are associated with neurologic symptoms (ie, hypotonia, ataxia, dementia, epilepsy, spasticity), sensory deficits (visual and hearing impairment), and nonneurologic features, such as gastrointestinal symptoms, dermatologic findings, atypical odor, and problems in growth. Specific metabolic testing includes acylcarnitine profile, amino acids and urine organic acids, glycosaminoglycans, oligosaccharides, serum total homocysteine, purines, pyrimidines, and GAA/creating metabolites. (2) Recent reports have identified 89 inborn errors of metabolism associated with ID that are amenable to treatment. In line with this, a 2-tiered algorithm in testing for treatable forms of inborn errors of metabolism in a person with ID has been proposed. (26) Further studies are needed to fully comprehend the efficacy and implications of this approach in the evaluation of a child with unexplained ID. (7)(27)

Magnetic resonance imaging (MRI) may be helpful in the evaluation of children with nonsyndromic ID/GDD in the setting of abnormal neurologic findings such as microcephaly, macrocephaly, or focal neurologic signs, (28) with the likelihood of finding a structural abnormality increasing to 28% from a rate of 7.5% if the GDD/ID was isolated and not associated with abnormalities in head size or focal neurologic findings. The risk in the use of sedation or anesthesia in MRI studies, although low, should also be weighed in the evaluation of these children. An MRI is preferred over computed tomographic (CT) scan in identifying abnormal brain architecture and myelination and in the evaluation of deeper brain centers. A CT scan is useful to visualize calcifications, which may be present in prenatal infections such as toxoplasmosis and cytomegalovirus.

DIFFERENTIAL DIAGNOSES

In the evaluation of persons suspected of having ID, it is important to differentiate ID from neurodegenerative disorders, specific learning disorders, receptive/expressive language disorders, autism spectrum disorders, and sensory deficits (visual impairment and hearing impairment).

Neurodegenerative disorders present with significant regression in different aspects of functioning due to a progressive neurologic condition. This is in contrast to ID, whose etiology is nonprogressive (eg, genetic abnormality or a nonprogressive brain lesion). Specific learning disorders are neurodevelopmental disorders characterized by persistent difficulties in learning (eg, reading, mathematics, and/or written expression) that are not explained by and are not commensurate with one's cognitive potential. Children with specific learning disorders can be differentiated from those with ID in that they may have impairment in specific areas of learning (eg, reading/phonological skills) but have age-appropriate adaptive skills and cognitive skills, whereas children with ID will have global impairment in cognitive and adaptive skills. Language deficits may also be present in ID, but in ID there are also significant nonverbal deficits, leading to a more global impairment in function. Autism spectrum disorder is frequently associated with ID but is a separate disorder characterized by persistent social-communication and social interaction deficits, restricted/repetitive patterns of behavior, and atypical sensory reactivities. (1) The cognitive level of children with autism may range from significant ID to normal intelligence. Last, in the evaluation of a child with suspected ID, it is important to rule out any significant visual and hearing impairment that may contribute to the child's deficits in functioning.

MANAGEMENT

Special Education and Early Intervention

The mainstay of treatment and management of children with ID/GDD is the utilization of special education and early intervention programs. (6)(29) The Individuals with Disabilities Education Act provides individuals with ID/GDD the right to receive free and appropriate public education with goals and services as specified in their Individualized Education Program (IEP) or Individualized Family Service Plan (for children <3 years old). Studies have shown that early childhood education programs have long-term beneficial effects on cognition, language, academics (reading and

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math), and youth behavior. (30)(31) There has been research as well showing that participation of children with ID (eg, Down syndrome) in early childhood educational programs may, at the very least, minimize the decline of intellectual functioning that occurs in these children. (32)(33)

During well-child visits, the pediatrician may detect developmental differences and delays through developmental surveillance or screening. Children who are suspected of having ID/GDD or other neurodevelopmental disorders should be referred to the state early intervention program (for children 0–3 years old) or to the Board of Education's Committee on Preschool Special Education (for children 3–5 years old) or Committee on Special Education (for children 5–21 years old) for evaluation and services.

The Individuals with Disabilities Education Act stipulates that children with disabilities receive their educational services in the least restrictive environment that is possible and appropriate to address their educational needs. Because of this, there has been a thrust toward mainstreaming wherein children with disabilities, even those with ID, may participate in more typical school environments for most or part of the school day. An inclusion or collaborative team teaching classroom is such a setting where children with special needs participate in the same classroom as typically developing children under the tutelage of 1 main teacher and 1 or more special education teachers. Children with disabilities may also receive related services such as speech/language therapy, occupational therapy, physical therapy, and counseling. In addition, classroom modifications and accommodations may be given to children with learning or intellectual disabilities through Section 504 of the Rehabilitation Act, (6) a federal law that protects individuals with disabilities from discrimination in various settings, including the public school system. Enhancing a person with ID's ability to communicate, not only through speech/language therapy but also through the use of a picture exchange communication system or augmentative communication devices, may be an important aspect of a child with ID's educational plan. Compared with typically developing children, children with ID learn at a much slower pace and may require more frequent repetitions before mastering a skill. Furthermore, the gap between these 2 groups will be increasingly wider as the years go by—an important tenet when counseling parents.

For children with more severe impairment, such as those with moderate to profound ID, a self-contained classroom may be needed wherein there is a small student to teacher ratio and the provision of individual or group paraprofessionals as needed. The child's IEP should reflect appropriate goals, which may be educational, vocational, or adaptive, while taking into consideration one's strengths and weaknesses. As the child reaches 16 years of age, the development of an Individualized Transition Plan would ensure continued support, beyond the educational realm, in areas such as employment, adult living skills, and recreation. (29)

Throughout this educational process, pediatricians play a key role, starting with the timely referral and identification of individuals with ID/GDD to being important advocates for their patients to receive services and interventions until they transition into adulthood. The Center for Parent Information and Resources (funded by the US Department of Education) offers helpful online information for pediatricians and parents about ID and the educational process, including the IEP and Individualized Transition Plan (http://www.parentcenterhub.org/intellectual/#school and http://www.parentcenterhub.org/transitionadult/).

Medical Home

The AAP and the US Department of Health and Human Services through its Healthy People 2010 have recommended that children, especially those with special health-care needs, which includes ID, receive "regular, ongoing, comprehensive care within a medical home." (34) In the medical home model of care, the pediatrician in collaboration with other medical subspecialists and professionals such as social workers and community health workers work as a team in the care of children with special needs, who, in addition to their primary disability, may have significant comorbid medical and psychiatric conditions and family challenges. The involvement of the family and addressing its needs are important components of the medical home.

Management of Comorbid Medical Conditions. Individuals with ID, especially those with moderate to profound ID, may have comorbid medical conditions such as seizure disorders, cerebral palsy, gastrointestinal disorders, and respiratory problems, which may have a significant effect on their daily functioning, progress, and need for additional support. (1)(5) Other important medical issues to explore in the care of people with ID are matters of sexuality and abuse, obesity and nutrition, physical activity and fitness, dental issues, and pain management. In addition to referring to appropriate subspecialists, the pediatrician has a role in providing information and resources to families about the child's disability, recommending healthy lifestyle options for diet and recreation, assuming the role of a conduit between the family and medical subspecialists, and being advocates for services that may address a patient's and family's needs. Online resources from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/intellectualdisability.pdf and https://www.cdc.gov/ncbddd/disabilityandhealth/healthyliving.html) and Parent Center

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Hub (http://www.parentcenterhub.org/find-your-center/) are examples of resources that may aid the pediatrician in this role.

Management of Comorbid Mental Health Conditions. Thirty percent of individuals with ID may have comorbid mental health conditions. (35) This rate is significantly higher than the rate observed in the general population. These mental health conditions include attention-deficit/hyperactivity disorder, depression, mood disorders, aggressive behaviors, and self-injurious behaviors. Behavioral interventions should be implemented in those with major behavioral difficulties, such as hyperactivity, aggressive behaviors, and self-injury. These interventions may be implemented in the home or school setting, with carryover to other settings to provide maximal benefit. Treatment with appropriate psychopharmacologic medications, based on target symptoms (eg, hyperactivity, aggressive behavior, self-injury), should be considered in those not fully controlled by behavioral measures, and referral to a child psychiatrist for medication management may be necessary.

Referral to State/Community Programs and Family Supports. It is important for the pediatrician to be aware of the state and community programs that are available for persons with ID and other developmental disabilities in their community. A social worker, who may be consulted within the practice (if available) or in community agencies, may be an invaluable resource in providing support for families and in directing them to the appropriate community programs. In New York State, children with significant ID and other developmental disabilities, such as autism, are directed to the New York State Office for People with Developmental Disabilities (https://opwdd.ny.gov/). After undergoing an eligibility evaluation, each child with a disability is assigned a service coordinator who assists the family in obtaining access to community programs, respite services, home care support and after-school programs, behavior-management training, transportation services, crisis intervention, etc. (36)(37) The pediatrician or social worker may also refer the child to entitlement programs such as Social Security and Medicaid, which may provide invaluable supports for families.

As a child with ID reaches adulthood, issues such as legal guardianship, transitioning to an adult health-care provider, and employment come to the forefront and must be addressed. There is growing research that shows that given appropriate support and guidance, persons with ID may strive for competitive or supportive employment. (29) With these educational, medical, and community interventions, the ultimate goal is for persons with ID to reach their maximum potential as individuals and as members of the community.

Summary

- According to the definition, intellectual disability (ID) is a neurodevelopmental disorder that is characterized by deficits in both intellectual functioning and adaptive functioning (>2 SD below the mean as measured by standardized tests and questionnaires), with onset in the developmental period or younger than 18 years of age. The severity of ID is based on a person's adaptive functioning and level of supports. (1)
- Based on some research evidence as well as consensus, the initial approach to the evaluation for the etiology of the ID includes a thorough history, a detailed physical examination, and a focused evaluation based on the history and physical examination findings, which may include laboratory testing, genetic testing, and imaging. (7)
- Based on some research evidence as well as consensus, the recommendation for the evaluation of nonsyndromic ID of unknown etiology includes genetic testing with chromosomal microarray analysis, fragile X testing, and karyotyping. For females with severe-profound ID, testing for Rett syndrome is also recommended. (24)
- Based on some research evidence as well as consensus, the mainstay of treatment and management of ID/global developmental delay is the utilization of special education and early intervention programs through the Individuals with Disabilities Education Act. Individuals with ID, especially those with moderate to profound ID, should also be evaluated for comorbid medical and mental health conditions, which are more prevalent in this population than in the healthy population. Finally, children with ID, as with other children with special health-care needs, are best followed in a medical home–type setting where there is collaboration between the pediatrician, other health professionals, community workers, and the child's family. (6)(29)(30)

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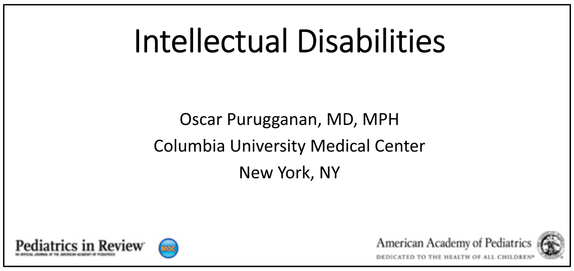

Intellectual Disabilities

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Pediatrics in Review

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1. A 7-year-old girl was noted to have global developmental delay by the time she was in preschool. She has been otherwise healthy, with no medical concerns. She has delays in reading, writing, and math skills and is very immature compared with her peers. These findings were not obvious in preschool and kindergarten, although she did receive early intervention for speech delay. Her academic delays have become more noticeable in second grade. Which of the following best describes this patient's intellectual functioning?
   - A. Borderline intellectual functioning.
   - B. Mild intellectual disability (ID).
   - C. Moderate ID.
   - D. Profound ID.
   - E. Severe ID.
2. A 10-year-old boy with moderate ID and autism is brought to your office for evaluation. His maternal uncle and maternal grandfather have ID. He was noted to have an elongated face. His mother has early-onset menopause. His medical history is unremarkable for any head trauma or central nervous system infections, and he has no history of seizures. Which of the following is the most appropriate next step in diagnosis in this patient?
   - A. Karyotyping.
   - B. DNA testing for fragile X syndrome.
   - C. Magnetic resonance imaging of his brain.
   - D. *MECP2* gene testing.
   - E. Whole exome sequencing.
3. After performing a thorough history and physical examination of the patient in question 2, you start the diagnostic evaluation, the results of which are still pending. Which of the following is most likely to be seen on physical examination of this patient?
   - A. Failure to thrive.
   - B. Lish nodules on eye examination.
   - C. Inguinal and axillary freckling.
   - D. Macrocephaly.
   - E. Skin ash leaf spot.
4. A 6-year-old girl has been diagnosed as having global developmental delay and macrocephaly. In the past year she has developed increased incoordination and ataxia as well as increasing academic challenges and marked difficulty learning new skills. The parents also report on and off gastrointestinal symptoms, including diarrhea, abdominal pain, and bloating. On physical examination she has no dysmorphic features and no abnormal physical findings. Which of the following is the most appropriate next step in diagnosis in this patient?
   - A. Chromosomal microarray analysis.
   - B. Fragile X testing.
   - C. Karyotyping.
   - D. Metabolic testing.
   - E. Whole exome sequencing.

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5. A 3-year-old boy uses approximately 20 words functionally. He can follow simple single-step instructions. He is not yet toilet trained and does not seem to understand the concept of toileting. He has a very short attention span but no significant behavioral concerns. You interview the family and note that there are no family members who have been identified as having developmental delays. On physical examination, his head circumference is at the 99th percentile. The remainder of his physical examination findings are within normal limits. Which of the following is the most appropriate next step in evaluation in this patient?
   - A. Acylcarnitine profile.
   - B. An electroencephalogram.
   - C. Magnetic resonance imaging of his brain.
   - D. Serum amino acids and urine organic acids.
   - E. Whole exome sequencing.

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Index of Suspicion

1 Abscess in a 9-year-old Boy

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Padem, Park, and Antoon have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 9-year-old Indian American boy presents to the clinic with buttock pain for 4 days. Associated symptoms include emesis and petechial rash for 2 days and intermittent confusion for 1 day. He has no history of surgical intervention, he is fully immunized, and his development is appropriate for his age. He was admitted to a PICU when he was 6 years old due to septic shock secondary to severe lymphadenitis. Family history is significant for asthma only. There is no family history of immunodeficiencies, severe infections, or early death. In a review of systems, the family report chronic dry cough for the previous few years.

In the clinic, the patient is found to be tachycardic, tachypneic, febrile, and mildly hypotensive. His oxygen saturation is normal on room air. Physical examination is significant for a buttock abscess and diffuse petechiae. Initial laboratory results demonstrate a normal complete blood cell count and basic metabolic profile and elevated levels of C-reactive protein, lactate, and coagulation factors (D-dimer and international normalized ratio). The patient is started on vancomycin and ceftriaxone. He is admitted to a PICU for further management.

On arrival at the PICU, he is noted to have hypotension. With a diagnosis of septic shock, he is started on epinephrine drip. Incision and drainage of a sacral abscess is performed, and wound cultures are positive for pan-susceptible *Staphylococcus aureus*. The patient improved and was discharged on oral antibiotics after a 6-day hospital stay. Concern for a second severe bacterial infection prompted an evaluation for possible immunodeficiency. Further laboratory testing reveals the diagnosis.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/6/310.

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DISCUSSION

The Condition

Pertinent laboratory results during hospitalization include negative human immunodeficiency virus, negative QuantiFERON®-TB Gold (Quest Diagnostics, Secaucus, NJ), normal nicotinamide adenine dinucleotide phosphate oxidase activity by dihydrorhodamine essay, undetectable CH50, very low immunoglobulin (Ig) G, and undetectable IgA and IgM levels (Table 1). Given his capillary leak and active infection, several immunology laboratory tests were repeated a few days later, and values remained low. Despite the fact that he was up-to-date on his immunizations, testing for specific antibodies against vaccine-associated antigens, including tetanus and diphtheria toxoid, *Haemophilus influenzae* type b polysaccharide antigens, and *Streptococcus pneumoniae* polysaccharide antigens, were all negative (Table 1). Lymphocyte marker analysis showed absent B cells. An in vitro lymphocyte mitogen stimulation study showed normal proliferative response. Genetic testing revealed W124R missense variant of the Bruton tyrosine kinase gene (*BTK*), confirming the diagnosis of X-linked agammaglobulinemia (XLA). The patient was started on intravenous immunoglobulin treatment every 4 weeks and remained free of infectious episodes 6 months after hospitalization.

X-linked agammaglobulinemia is a primary immunodeficiency characterized by abnormal B cell maturation and differentiation. It was first described by Bruton in 1952 and is the result of mutations involving the *BTK* gene. (1)(2)(3) Currently there are more than 300 mutations described, leading to highly variable presentations and disease courses. (4) X-linked agammaglobulinemia is a rare disease with an incidence of 1 in 379,000 live births in the United States. (5)

TABLE 1. **Laboratory results at the time of diagnosis**

	RESULT	NORMAL	UNITS
IgG	324	608–1572	mg/dL
IgA	3	34–274	mg/dL
IgM	11	38–251	mg/dL
Specific antibodies to			
Tetanus toxoid, IgG	0.0	>0.1	IU/mL
Diphtheria toxoid, IgG	0.0	>0.1	IU/mL
Haemophilus influenzae B, IgG	0.0	>0.1	IU/mL
Pneumococcal polysaccharide 23 serotypes, IgG	<0.3	>1.3	μg/mL
Isohemagglutinin titers	Absent anti-A (patient's blood group B+)		
CH50			
During sepsis	0	60–144	CAE
After resolution of sepsis	103	60–144	CAE
Lymphocyte subsets			
Absolute CD4	2349	430–1800	cells/μL
Absolute CD3	6453	570–2400	cells/μL
Absolute natural killer cells	242	78–470	cells/μL
Absolute CD19	<1	91–610	cells/μL
Neutrophil oxidative burst	Normal nicotinamide adenine dinucleotide phosphate oxidase activity by dihydrorhodamine essay		
In vitro lymphocyte stimulation study	Normal lymphocyte responses to *Candida*, tetanus, phytohemagglutinin, con A, pokeweed mitogen		
BTK gene mutation test	W124R missense variant in the *BTK* gene		

Ig=immunoglobulin.

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Clinical Manifestations

The classic presentation of XLA consists of recurrent and/or severe infections after the loss of maternal immunoglobulins in blood at approximately 3 to 6 months of age. A report of data from 201 patients in the United States showed that the most common presentation or information that led to the initial diagnosis of XLA is increased susceptibility to infection (86%), followed by family history (41%). (5) The same study also showed that more than 50% of cases were symptomatic before age 1 year and 50% of cases were diagnosed as having hypogammaglobulinemia or agammaglobulinemia by 2 years of age. Patients with a family history of XLA were diagnosed earlier (mean, 2.59 years) compared with patients with no family history (mean, 5.37 years). Although the classical diagnosis age is in early childhood, there are case studies reporting presentation in adulthood. (6)

The most common infections associated with XLA are otitis media, pneumonia, sinusitis, diarrhea, conjunctivitis, sepsis, and cellulitis. One-third of XLA diagnoses are made after a severe infection, such as sepsis, meningitis, cellulitis, and empyema. (4)(5) Rarely, these patients may develop vaccine-related paralytic poliomyelitis. (4)(7) Although immune modulation against viruses seems to be intact in XLA, echovirus infections are a well-known cause of encephalitis and meningitis in this population. (5)(6)(8)

Diagnosis

Diagnosis of XLA includes very low levels of all immunoglobulin isotypes, a very low number or absent B cells in peripheral blood, and molecular studies showing mutations in the *BTK* gene. Although lack of lymphoid tissue is a common feature of the disease, presence of lymphoid tissue does not rule out XLA diagnosis. (1)(11)(12)(13) The sentinel XLA case described by Bruton was a male child who underwent adenotonsillectomy and was found to have lymphoid and tonsillar tissue. Kornfeld et al (14) additionally reported a case with a history of adenotonsillectomy. Our patient was admitted to the hospital with severe lymphadenitis at 6 years of age and was noted to have lymphoid and tonsillar hypertrophy on physical examinations in his medical history, confirmed with CT scans and radiographic imaging at age 6 years (Figs 1 and 2).

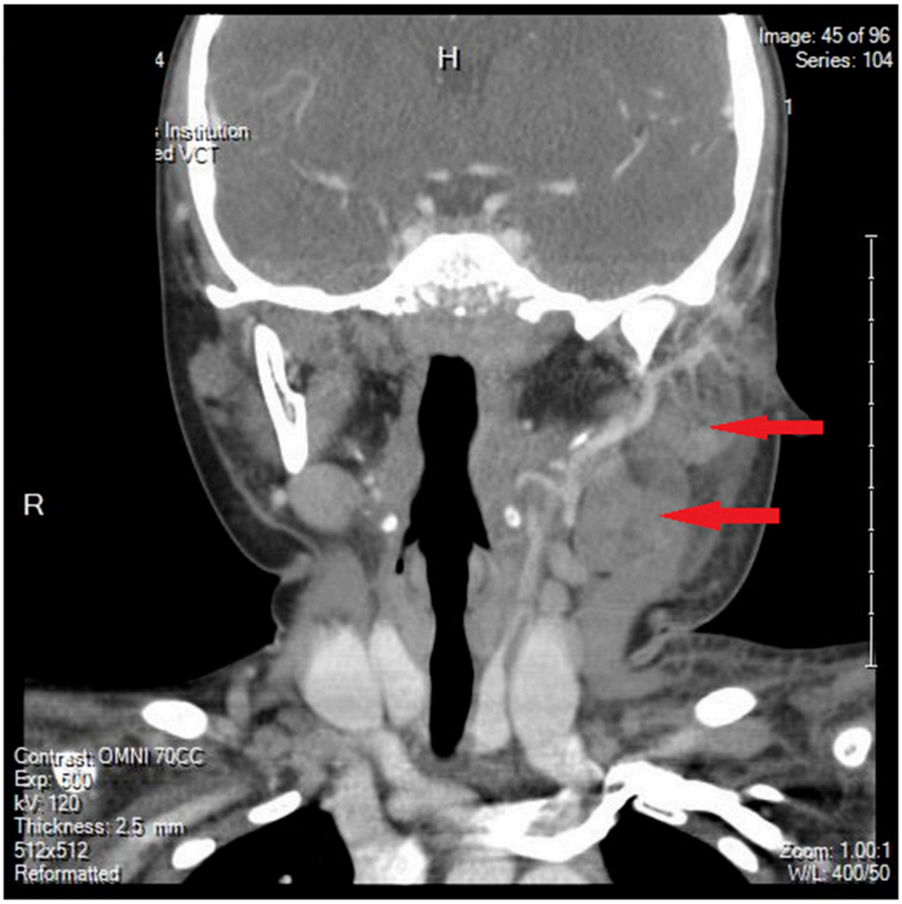

Figure 1. Lymphadenitis shown on a computed tomographic scan of the head and neck.

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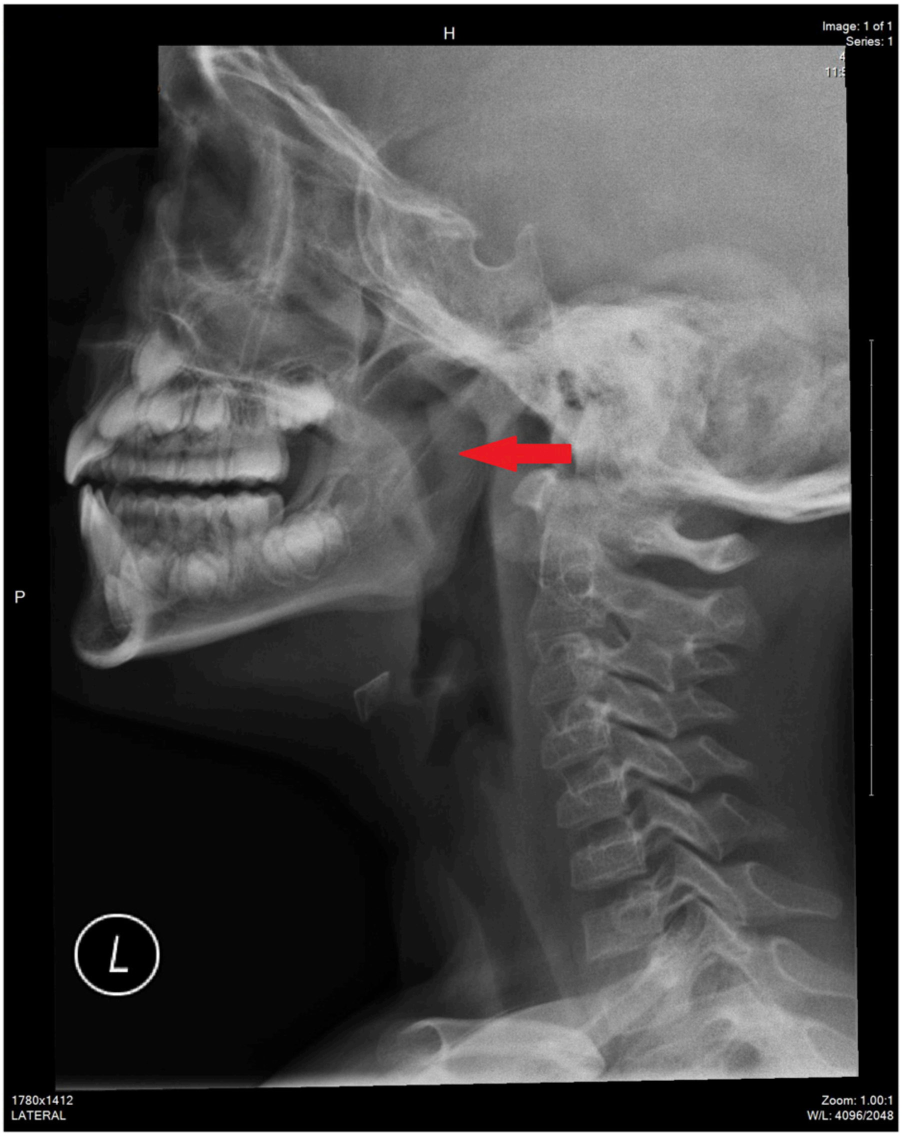

Figure 2. Lateral neck soft tissue radiograph with mildly prominent palatine tonsil and normal thickness of prevertebral soft tissue.

Delayed diagnosis of XLA can result in long-term chronic complications, such as bronchiectasis and other life-threatening infections. An immunologic evaluation was not performed for our patient when he was admitted to the hospital for sepsis secondary to lymphadenitis. The presented case highlights that the presence of lymphoid or tonsillar tissue and older age do not exclude XLA. This variation might be a result of multiple mutations of the *BTK* gene affecting disease process and presentation. Clinicians should have a high suspicion of XLA in male patients with severe or recurrent infections.

Management

A variety of malignancies are documented in patients with XLA, but a correlation between certain tumors and XLA has not been proved. (5)(9)(10) Treatment of XLA remains immunoglobulin replacement with regular intravenous immunoglobulin or subcutaneous immunoglobulin infusions. Prophylactic treatment of infections with antibiotics remains controversial.

Lessons for the Clinician

- Patients with recurrent sinopulmonary infections, unexpectedly severe disease courses, or infections with uncommon pathogens at any age should be evaluated for primary immunodeficiency diseases, including X-linked agammaglobulinemia (XLA).
- Infections caused by live viral vaccines should also raise suspicion for immunodeficiency.
- Patients with XLA classically present with minimal lymph tissue and usually absent tonsillar tissue, but the presence

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of lymphoid or tonsillar tissue should not exclude a diagnosis of XLA.

- Late diagnosis of XLA can result in early bronchiectasis, leading to worsening lung function, recurrent infections resulting in multiple hospital admissions, growth and development delay, missed school/work days, and eventually an increase in mortality.

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Case 1: Abscess in a 9-year-old Boy

Nurcicek Padem, Lucy Park and James W. Antoon

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Index of Suspicion

2 Red Toes in a 17-day-old Boy

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AUTHOR DISCLOSURE Drs Sears, Perez, and Shriner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 17-day-old boy is admitted to the hospital due to erythema of bilateral halluces. On the day of admission, he first was taken to an urgent care facility for this issue, where the mother was advised to bring him to the pediatric emergency department for the evaluation of possible herpetic whitlow. His mother first noticed that both of his big toes were becoming progressively "more red than usual" over the past week. He is eating, urinating, and defecating normally. There has been no fever, diarrhea, vomiting, inconsolability, or rash, and he is developing normally. He is not exhibiting signs of experiencing pain. Mom does occasionally get fever blisters. She has not trimmed the toenails in question due to inability to access them.

On presentation he is afebrile and his vital signs are within normal limits. He appears well. Physical examination is significant only for erythematous distal halluces, with the distal nails coursing beneath the inflamed tissue.

A quick bedside search of the medical literature is performed and reveals the diagnosis, obviating antiviral therapy and further laboratory/radiologic evaluation.

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/6/311.

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DISCUSSION

The diagnosis in this case is congenital ingrown toenail of the hallux (CITH) (Figs 1–4), grade 2 variation by the classification system of Honig et al. (1) It is an entity that begins in utero when the distal nail bed of the hallux is short and becomes entrapped in an overabundance of normal soft tissue. The grading system is described as follows: normal—nail plate is growing out over the end of the toe without impedance by tissue; grade 1 variation—the nail plate is curved at its distal end growing up and over the tissue at the distal end of the great toe; and grade 2 variation—the distal end of the nail plate appears to be growing right into the tissue at the distal end of the great toe. (1) The noted erythema occurs as the nail plate grows through the distal tissue, inducing local inflammation with formation of granulation tissue. It has been noted that once the nail plate successfully migrates to its normal length, the redundant superior tissue simply falls off.

There are a limited number of studies available in the literature to guide clinicians in the diagnosis and management of this condition. The prospective study by Honig et al in 1982 (1) has proved to be one of the most influential. In this study, 302 newborns that were admitted to the normal newborn nursery were followed for 1 year. Seventeen percent of these children were found to have a grade 2 variation similar to our patient. By 6 months, all grade 2 variations had spontaneously resolved without intervention, and they had no increased risk of paronychia, suggesting that this finding was a normal variation. (1)

Authors have variously described both inherited patterns and sporadic occurrences, likely due to the capability of different processes of malformation to produce similar findings. The study by Honig et al (1) did not identify an inheritance pattern.

The differential diagnosis should include, as noted appropriately by other clinicians in this case, herpetic whitlow and paronychia. Other congenital nail malformations can present similarly, such as that described by Chapman et al (2) where the nail growth plate is angularly skewed and overgrowth can occur. The differing inheritance pattern and differing nail plate pathology indicate, however, that these findings are part of a separate pathological process that did lead to predisposition to paronychia as young adults but not as infants.

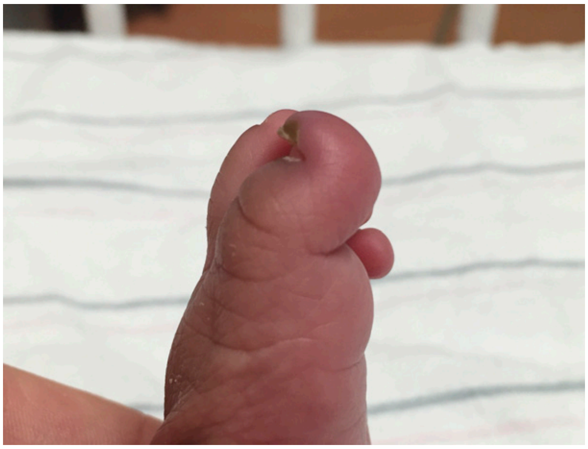

Figure 2. Medial view of the left hallux.

Management suggestions have similarly varied in the literature. Honig et al (1) showed that conservative management with observation led to complete resolution of the grade 2 CITH by 6 months of age. Others, including Grassbaugh et al, (3) reported persistent cases requiring surgical correction by “fish-mouth incisions” and resections of the “distal tufts of soft tissue in which the nail plates were incarcerated.” All operations were successful without recurrence. The exact type of overgrowth is also likely important given that end-on overgrowth, as in our patient, may behave differently than lateral overgrowth. Regardless, there is strong consensus that the first line of therapy should be

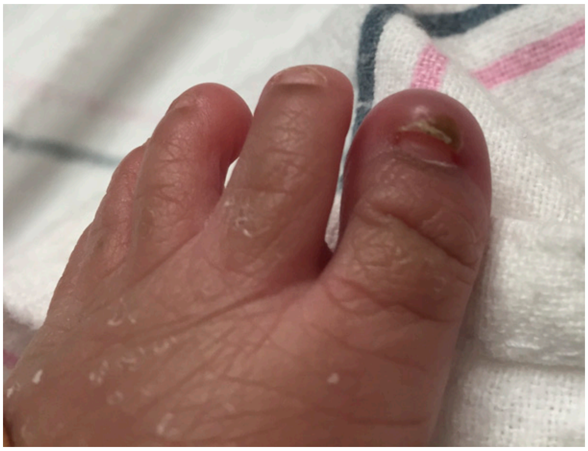

Figure 1. Dorsal view of the left hallux.

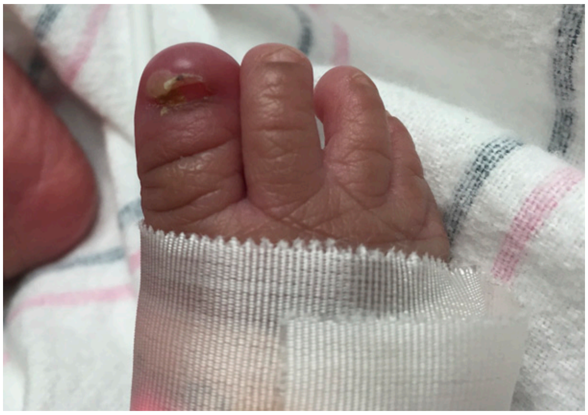

Figure 3. Dorsal view of the right hallux.

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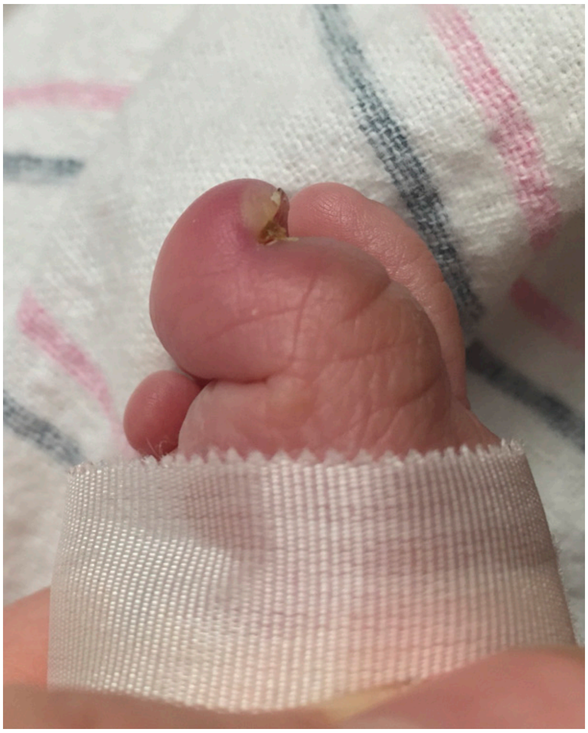

Figure 4. Medial view of the right hallux.

observation. Some clinicians believe that the erythema warrants antibiotic therapy due to concern of concomitant paronychia, whereas others believe that this is unnecessary.

Outcome

Our patient presented with distinctive bilateral nail findings coincident with erythema that prompted us to search for alternative causes. A bedside literature search readily revealed the correct diagnosis to be CITH. The plastic surgery department was consulted, and conservative management was recommended. The case was successfully managed without antibiotic therapy, with normalization of bilateral halluces by 6 months of age.

Lessons for the Clinician

- A close examination of the nails for malformation is warranted in any infant presenting with erythematous digits.
- Congenital ingrown toenail of the hallux, a relatively less discussed diagnosis, should be included in the differential diagnosis of infantile erythematous halluces.
- Most commonly, observation with conservative management is successful. There is a potential need for surgical consultation after 6 months, or sooner in consultation with parents, if resolution does not occur spontaneously.

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Case 2: Red Toes in a 17-day-old Boy

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Index of Suspicion

3 Acute Hypotonia, Hypothermia, and Altered Mental Status in a 10-month-old Girl

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AUTHOR DISCLOSURE Dr Beardmore has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr Beardmore is now in private practice with SSM Health/Dean Pediatrics in Janesville, WI.

PRESENTATION

A 10-month-old previously healthy girl presents to the emergency department after being found unresponsive by her parents. The parents report she was a little fussy last night when they put her to bed, but it was not out of the ordinary. This morning she was found unresponsive to verbal or physical stimuli, completely limp, and blankly staring, and they immediately rushed her to the hospital. She has no medical problems, takes no medication, has had regular follow-up with her pediatrician, and all her shots are up to date. She has been hospitalized only once previously, a less than 3-day stay before turning 1 month old, for a fever and to rule out sepsis. She was then discharged with normal laboratory values and only 2 days of antibiotic drug therapy for a presumed viral illness.

On arrival at the emergency department her immediate general assessment shows her eyes open and blankly staring, with complete loss of tone. Her vital signs include rectal temperature of 95.3°F (35.2°C), heart rate of 100 beats/min, respiratory rate of 30 breaths/min, pulse oximetry of 100% on room air, and blood pressure of 123/77 mm Hg. Her heart examination findings are normal, and her capillary refill is not prolonged. She has normal nonlabored respirations with clear breath sounds, and her abdomen is soft without organomegaly or masses palpated. Her conjunctivae are without pallor, and her mucous membranes are moist. Her anterior fontanelle is open and flat, not bulging or sunken, and she has no neck stiffness. Her pupils are mid-sized and do not respond to light. She has a blink reflex to light but not to visual threat. She has only minimal whimper to sternal rub. All 4 extremities are floppy, with 0/5 strength, and she has complete head lag when her torso is lifted. Her deep tendon reflexes are normal. Her secondary survey shows no bony or joint deformities, swellings, or other abnormalities; her skin examination findings are normal, without lesions, ecchymosis, or areas of erythema; her genitourinary examination findings are also normal. Initial laboratory investigations and follow-up history reveal the diagnosis.

The Case Discussion and Reference appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/6/312.

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DISCUSSION

The first laboratory test performed on this hypothermic child with altered mental status was a finger-prick glucose test (to which she did not react or withdraw), and the value was 18 mg/dL (1 mmol/L). A peripheral intravenous line was placed, and during the administration of 50 mL (5 mL/kg) of dextrose 10% in water (D10W) she began to first blink, then voluntarily move extremities, then cry, and by the end of the infusion, in a matter of only a few minutes, she was looking and reaching for her parents. Further questioning elicited that the paternal grandmother lives in the home and has type 2 diabetes, and the father states that he found spilled tablets on the floor in the home 2 days ago. When the child was stable, the father was able to go home and procure the medicine he had cleaned up. The bottle label showed that it was 10-mg glipizide. It was, therefore, assumed that the father must have missed 1 or more of the spilled tablets when cleaning up and the child was able to find and ingest 1. This hypothesis was strengthened when the follow-up glucose values improved and then dropped again, improving to 201 mg/dL (11.2 mmol/L) after the first D10W bolus and dropping again to 41 mg/dL (2.3 mmol/L), although she stayed asymptomatic at this value.

The Condition

Hypoglycemia caused by ingestion of a sulfonylurea is due to endogenous insulin release. Sulfonylureas inhibit potassium channels of pancreatic β cells, leading to intracellular potassium increase, depolarization of the cell, calcium influx, and, finally, insulin release from the pancreas. The time to peak onset, the half-life, and the duration of action of sulfonylureas are specific to each drug, and for glipizide they are approximately 1 to 3 hours, 2 to 5 hours, and 16 to 24 hours, respectively. (1) Octreotide is the antidote to this because it works as a semisynthetic somatostatin analog that inhibits pancreatic insulin release. The appropriate dose in children is 1.0 to 1.5 μg/kg per dose given intramuscularly, subcutaneously, or by intravenous bolus, repeated every 6 hours for the expected duration of action of the ingested drug. (1)

When correcting hypoglycemia with an intravenous bolus, whatever the cause, a good rule to remember is the rule of 50s. That is, in a formula multiplying dextrose percentage by volume in milliliters per kilogram, the value should always equal 50: $\text{D}\ a\ \% \times b\ \text{mL/kg} = 50$, choosing a percentage a and solving for b. In our case, choosing D10W resulted in a need for 5 mL/kg, so for a 10-kg child, the bolus is 50 mL. If D5W were chosen, a volume of 10 mL/kg would equal the rule number of 50, and thus for a 10-kg child, the bolus would need to be 100 mL, which may be preferred if increasing intravascular volume would also be helpful.

Management and Patient Course

In consult with the toxicologist before the grandmother's medication could even be determined, the child's case presentation was suspicious for ingestion of a sulfonylurea. After rebound hypoglycemia to a glucose level of 41 mg/dL (2.3 mmol/L), which required a second D10W bolus in addition to continuous dextrose infusion, and confirmation of the spilled glipizide in the home, the toxicologist recommended octreotide subcutaneous injection, a total of 5 μg/kg divided into 4 injections, spaced every 6 hours, to cover the expected maximum of 24 hours of duration of action. The child received her first injection in the emergency department and was admitted to the ICU for mental status and glucose level monitoring. Owing to her hypothermia on arrival, which improved along with the immediate correction of her hypoglycemia, laboratory testing was conducted to rule out serious bacterial infection at the time of the initial presentation, and all the results were normal, including a negative blood culture. The child was discharged after 24 hours, after the last octreotide injection, without a further episode of hypoglycemia and without a return of altered mental status.

Lessons for the Clinician

- Blood glucose is often a valuable initial test when evaluating a child with altered mental status.
- Altered mental status from hypoglycemia can be accompanied by significant neurologic findings and hypothermia.
- Uncovering the cause of the hypoglycemia is of utmost importance for treatment purposes and should, thus, include a detailed and thorough history.

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Case 3: Acute Hypotonia, Hypothermia, and Altered Mental Status in a 10-month-old Girl

Dan Beardmore

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Case 3: Acute Hypotonia, Hypothermia, and Altered Mental Status in a 10-month-old Girl

Dan Beardmore

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Stroke after Minor Trauma in an Otherwise Healthy 18-month-old Boy

Cherilyn Cecchini, MD,* Sabah Iqbal, MD,† Jonathan Murnick, MD, PhD*

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AUTHOR DISCLOSURE Drs Cecchini, Iqbal, and Murnick have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 18-month-old boy presents to the emergency department (ED) after a fall. His parents reported that the father was carrying the child down the stairs when he slipped 1 step from the bottom; the child fell out of his arms and landed on his chest on the hardwood floor. The child did not lose consciousness and he cried immediately, but several minutes later his mother noticed that he seemed "dazed." Emergency medical services was called, and the child was alert and awake on their arrival.

The child arrived at the ED 3.5 hours after the fall given the family's remote location. During his initial examination he was sitting in his mother's arms with his head held midline and was moving all 4 extremities. The remainder of his examination findings are normal. His mother is very worried that "something" is wrong. He is stratified as intermediate risk for traumatic brain injury, and the decision is made to observe him in the ED.

After a trial of oral intake, he stood up to walk, at which point he is noted to be slightly antalgic. Shortly after that his mother notices right-sided facial droop when he smiles and that his head is tilted to the left. The physician notes decreased movement of the right arm and leg, with only a weak grip in his right hand. A Miami J collar is placed, and head computed tomographic (CT) scans and C-spine radiographs are ordered. The head CT scan reveals the diagnosis. The child is hospitalized in the ICU.

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DISCUSSION

Differential Diagnosis

Differential diagnosis included intracranial hemorrhage, arterial ischemic stroke, acute arterial dissection, and nonaccidental trauma.

After the change in neurologic status, diagnostic studies were performed; C-spine radiographs were negative, and an electrocardiogram showed normal sinus rhythm. A noncontrast CT scan of the head revealed a small chronic infarct of the left caudate head and scattered mineralization in both lateral putamina. It was suggested that the imaging findings and clinical history were most consistent with lenticulostriate mineralizing angiopathy with infarct after minor trauma. The visualized chronic infarct likely represented a previous subclinical stroke, and the presenting symptoms raised suspicion for a new acute basal ganglia infarct not yet visible by CT scanning. Acute infarct was confirmed by magnetic resonance imaging.

The patient underwent a full thrombophilia evaluation because there was a family history of stroke in an uncle at a young age. He was started on aspirin 80 mg by mouth in the ED.

The Condition

Basal ganglia stroke after minor trauma associated with mineralizing angiopathy is an uncommon phenomenon in children, but it is a unique clinicoradiologic entity. (1) The particular findings have been described by previous authors in several case studies and brief series. This specific kind of infarct after minor trauma accounts for less than 2% of all childhood ischemic stroke. (2) The classic age range is described as younger than 18 months but can extend to as old as 26 months. (1) The condition also does not seem to demonstrate cultural or ethnic predisposition. (1) It does, however, seem to have an elevated incidence rate in boys. (1)(3)

Pathophysiology

The pathophysiology is largely unknown, with many proposed theories. Yang et al (3) suggest that the angle between the main middle cerebral artery and the lenticulostriate arteries, which supply the basal ganglia and internal capsule, is more acute in infancy and early childhood and, therefore, more prone to ischemia. (3)

Other authors have suggested that central nervous system cytomegalovirus infection is a risk factor for stroke in the setting of basal ganglia calcification. (3) It is unclear whether CMV infection can itself cause basal ganglia mineralization. (1)

Diagnosis

History and physical examination typically include details of a minor trauma or fall. Hemiparesis and facial paresis occur within 72 hours after the initial insult. (1)(2)(3)(4) Some cases described also report associated convulsion. (4) Typically, there is no evidence of hypercoagulability or an underlying thrombophilic condition. (1) This mineralizing angiopathy is typically visualized on CT scans without contrast, (1) making this modality necessary for diagnosis. The Figure highlights these findings.

Lingappa et al (1) also showed that magnetic resonance imaging studies do not always identify the characteristic mineralization. Furthermore, standard CT scanning does not always reveal the true extent of the vascular mineralization. Therefore, one should consider thin-section spiral CT scans with multiplanar reconstructions, (1) especially if clinical suspicion remains high and other imaging studies are unrevealing.

Management and Prognosis

Conservative treatment is typically the most effective management of choice for basal ganglia stroke in the pediatric population. A review of the literature shows that existing consensus statements do not recommend anticoagulation for children with microvascular disease. Patients are provided with close monitoring and physical therapy. (1)(2)

It has been demonstrated that short- and long-term neurodevelopmental outcomes are good. Although some children demonstrate minor weakness or deficits in their gross motor skills, these tend to improve over time. (1) Most often, hemiplegia typically disappears within 24 hours of presentation. Dharker et al (5) showed that all but 1 of 23

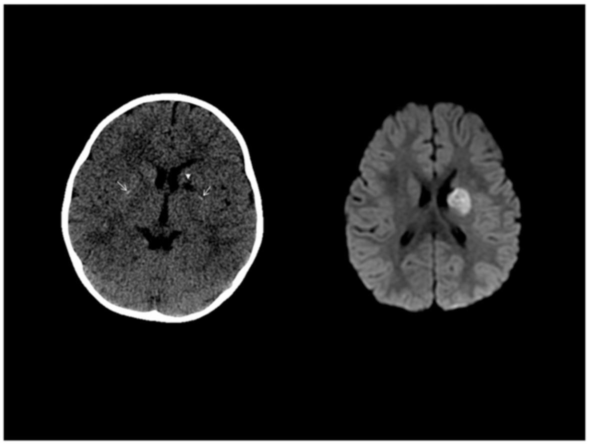

Figure. Left, Axial noncontrast computed tomographic scan demonstrating small linear calcifications in both putamina (arrows) and small chronic infarct involving the left caudate head and internal capsule (arrowhead). Right, Diffusion-weighted magnetic resonance image from the same day demonstrating a larger acute left basal ganglia infarct.

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children who developed immediate unilateral weakness after minor head injury recovered completely within 4 months. Although most strokes in this condition are solitary events, a substantial minority of patients experience recurrent events (23% in the largest published series). With recurrent stroke, outcomes are worsened and may include continued hemiparesis and speech delay with fine motor difficulties. (6)

Lessons for the Clinician

- Ischemic stroke is a rare complication of minor head trauma in pediatrics.
- Consider mineralizing angiopathy in a child presenting with minor head trauma and signs of stroke, specifically hemiparesis or facial paresis shortly after the incident.
- Children with mineralizing angiopathy are not typically found to have laboratory findings supportive of an underlying thrombophilic state.
- In the acute period, a combination of noncontrast head computed tomographic scanning (to demonstrate mineralization) and magnetic resonance imaging (to demonstrate acute infarct) is often necessary for diagnosis.
- Conservative treatment and close monitoring generally result in good outcomes for children with mineralizing angiopathy and subsequent basal ganglia stroke after minor trauma.

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Cherilyn Cecchini, Sabah Iqbal and Jonathan Murnick

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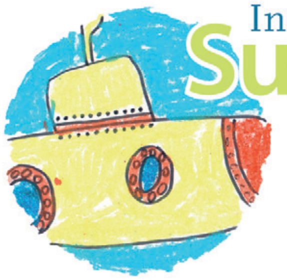

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5 Acute Behavioral Changes in a 17-year-old Girl

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AUTHOR DISCLOSURE Drs Kader, Ngiam, and Kao have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl is brought to the emergency department for unusual behaviors. On the day of presentation, her family members found her intermittently crying and talking to herself about angels, demons, redemption, and sins. She was speaking in a different voice and telling her family of "something evil within her." Her parents sought spiritual help from a priest, but this failed to improve her behavior. There were no recent changes in her mood, behavior, or academic performance.

The patient is overweight but otherwise well. For the past month she has taken slimming pills from an online store, but no other medications. She is a high-achieving student. She denies smoking, alcohol intake, or illicit drug use. There is no family history of psychiatric disorders.

On examination, she is clutching her crucifix, smiling, and laughing inappropriately. Her temperature is 98.6°F (37°C), heart rate is 101 beats/min, blood pressure is 120/61 mm Hg, respiratory rate is 18 breaths/min, and oxygen saturation is 99% on room air. Her weight is 167 lb (75.8 kg) (>97th percentile), height is 63.4 in (1.61 m) (75th-90th percentile), and BMI is 29.2. Her heart, lungs, and abdomen are normal. Findings from examination of the cranial nerves, tone, and reflexes are normal. She intermittently engages in conversation, describing multiple voices that interrupt her thoughts and tell her to hurt herself and her family.

She is admitted to the psychiatric ward. Laboratory test results, including a complete blood cell count; renal, liver, and thyroid function tests; complement 3 and 4 levels; ceruloplasmin levels; and urine drug screen, are normal. Further investigations reveal the diagnosis.

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DISCUSSION

This girl has had an episode of acute psychosis, with auditory hallucinations, persecutory delusions, and thought interference.

The differential diagnosis of acute psychosis is broad. For such an acute onset, drug-induced hallucinosis must be considered. The initial urine analysis may be limited in the range of substances that can be tested for. Thus, any suspected substances that the patient is taking should be sent for further analysis.

Complex partial seizures may manifest as changes in behavior and affect and may be difficult to distinguish from primary psychiatric disorders. An electroencephalogram should be performed to determine whether episodes of unusual behavior correlate with seizure activity.

Although rarer and less likely, any cause of encephalopathy, including neurodegenerative disorders, space-occupying lesions (brain tumors, abscesses), demyelinating disorders (acute demyelinating encephalomyelitis, multiple sclerosis), and immune-mediated causes, such as anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis, may also be responsible for behavior changes and psychiatric symptoms.

Systemic medical conditions associated with neuropsychiatric manifestations include systemic lupus erythematosus; hyperthyroidism and hypothyroidism; metabolic disorders such as Wilson disease and acute intermittent porphyria; infections such as human immunodeficiency virus and syphilis; and postinfectious syndromes. However, the clinical course is frequently of repeated episodes or progressive worsening. There are also often other physical signs or abnormal laboratory results to suggest the underlying etiology.

Finally, this may be the first presentation of a primary psychotic disorder such as schizophrenia, but this would be more likely to have a more chronic course. A brief psychotic episode—defined as a sudden onset of psychosis of less than 1 month and a full return to normal functioning thereafter—may be a possibility. The patient's cultural and religious background must also be considered when deciding whether a patient's beliefs are truly delusional.

A summary of these conditions and the relevant investigations are listed in the Table.

During her inpatient stay, the electroencephalogram showed a normal background and no epileptiform activity, even during her auditory hallucinations. She also underwent brain magnetic resonance imaging, with normal findings. Additional blood investigations for antistreptolysin O antibodies and anti-NMDA receptor antibodies were negative.

She is started on risperidone therapy but is discharged against medical advice 3 days later because her parents feel that the problem is spiritual rather than medical.

TABLE. **Differential diagnoses for a first psychotic episode**

CONDITION	METHOD OF DIAGNOSIS
Neurologic	
Neurodegenerative disease Space-occupying lesion (tumor, abscess) Demyelinating disease Immune-mediated encephalitis	Brain magnetic resonance imaging Lumbar puncture (oligoclonal bands, *N*-methyl-D-aspartate receptor antibodies)
Systemic conditions with neuropsychiatric manifestations	
Systemic lupus erythematosus	Complements 3 and 4, anti-dsDNA
Hyperthyroidism/hypothyroidism	Thyroid function test
Wilson disease	Serum ceruloplasmin
Acute intermittent porphyria	Urine porphobilinogen
Infections (human immunodeficiency virus, syphilis)	Enzyme-linked immunosorbent assays for human immunodeficiency virus VDRL test for syphilis
Psychiatric Schizophrenia Bipolar disorder Schizoaffective disorder	Psychiatric assessment
Cultural	Explore patient's belief systems

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The slimming pills are sent to the Health Sciences Authority for further analysis. Although the pills were touted to contain only "all-natural ingredients," such as grapefruit and green tea, they are, in fact, found to contain undeclared amounts of sibutramine, a drug that has been banned in Singapore. A public health warning about the pills has been made in the local media.

The Condition

Many drugs are known to cause psychotic symptoms. The best known of these are alcohol and recreational drugs such as lysergic acid diethylamide (LSD), cocaine, cannabis, and amphetamines. However, other prescription drugs have been implicated as well, including opiates, selective serotonin reuptake inhibitors, barbiturates and benzodiazepines, clarithromycin, quinolone antibiotics, proton pump inhibitors, and sibutramine. Over-the-counter medications such as dextromethorphan and antihistamines at high doses have also been implicated in psychosis.

Sibutramine is a serotonin and norepinephrine reuptake inhibitor structurally related to the amphetamines. Its serotonergic action enhances satiety, and thus it had been marketed extensively as an anti-obesity agent. However, the Sibutramine Cardiovascular Outcomes (SCOUT) randomized controlled trial demonstrated increased risk of cardiovascular morbidity associated with sibutramine, confirming the concerns highlighted in previous case reports. Other common adverse effects of sibutramine include insomnia, dry mouth, constipation, nausea, and headache.

Sibutramine has since been withdrawn from the market in many countries around the world. Nevertheless, it is a common, undeclared ingredient in many weight-loss products that can be bought over the counter and from online stores. Examples of such products include "Slim Fit X," a product with a Food and Drug Administration (FDA) warning issued on July 27, 2016; "Zi Su Body Fat Health II," FDA warning issued on October 26, 2016; and "Nutri Drops Grapefruit Diet," warning issued in 2014. The dose of the drug in question should be checked if possible; there have been reports of illicit drugs in over-the-counter products being included in doses 3 or more times the recommended medical dose.

Sibutramine-associated psychosis has been well-documented in case reports and case series. The psychotic symptoms are attributed to increased dopamine levels due to reuptake inhibition, and the psychopathology includes manic episodes, delusional disorders, paranoid episodes, suicidal ideations, and catatonia. In a relatively large series from Hong Kong involving 16 patients, the most common psychiatric manifestations were auditory hallucinations, visual hallucinations, and persecutory ideations. These symptoms are self-remitting after stopping sibutramine use.

Management

A thorough evaluation for organic medical conditions associated with psychiatric manifestations should be performed. A comprehensive medication history inclusive of alternative, traditional, or over-the-counter substances and illicit drugs is of great importance. Such substances should be analyzed at a specialized laboratory to determine their constituents.

Treatment consists of immediate cessation of the offending agent(s). Antipsychotic agents may be used for a short period. Resolution within several days is expected, but patients should be followed up to ensure that psychotic symptoms do not recur.

To prevent further cases, the public must be educated about the risks of buying slimming products over the counter or from online sources and to be aware that such products often contain undeclared drugs that are hazardous to health.

On outpatient review 2 weeks after hospitalization, the patient's auditory hallucinations and delusions had resolved. She and her family have been informed about the contents of the slimming pills, and she has stopped taking these pills since her inpatient admission.

Lessons for the Clinician

- Drug-induced psychosis must be in the differential diagnosis for a patient presenting with acute psychosis.
- The differential diagnosis of psychotic symptoms is wide, and patients should be thoroughly evaluated for underlying medical causes before attributing the psychosis to a primary psychiatric disorder.
- The public must be made aware that substances banned by the health authorities may still be present in slimming products bought from online stores or over the counter.

Suggested Readings

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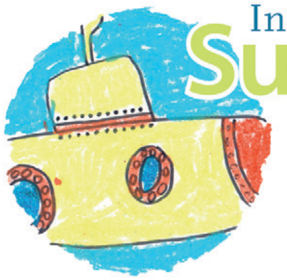

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6 Liver Failure and Rash in a 6-week-old Girl

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AUTHOR DISCLOSURE Drs Mediratta, Schwenk, Rao, and Chitkara have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 6-week-old girl is admitted to the NICU with liver dysfunction and jaundice. One week before presentation she had developed an erythematous macular rash on the chest and extremities, oral thrush, and a low-grade fever. Physical examination reveals jaundice, hepatosplenomegaly, and a desquamating macular rash on the left lower extremity. Her vital signs are normal for age. She was born to a 34-year-old G7P2321 woman via normal spontaneous vaginal delivery at 37 weeks' gestation. Birthweight was 3,060 g (35th percentile). The infant's mother had routine prenatal care, and her course was complicated by intrahepatic cholestasis of pregnancy. Results of first-trimester maternal *Treponema pallidum* enzyme immunoassay were negative.

Laboratory evaluation reveals acute liver failure, coagulopathy, conjugated hyperbilirubinemia, lymphocyte-predominant leukocytosis, disseminated intravascular coagulation, anemia, and thrombocytopenia. Laboratory test results are notable for hemoglobin level, 7.2 g/dL (72 g/L); total leukocyte count, 25,000/μL (25.0×10^9/L) with 68% lymphocytes and 18% neutrophils; platelet count, $20 \times 10^3/\mu$L (20×10^9/L); aspartate aminotransferase, 1,164 U/L (19.4 μkat/L); alanine aminotransferase, 536 U/L (8.9 μkat/L); albumin, 1.8 g/dL (18 g/L); international normalized ratio, 1.8; and partial thromboplastin time, 34.9 seconds. Her C-reactive protein level was elevated at 19.1 mg/L (181.9 nmol/L).

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DISCUSSION

The differential diagnosis includes sepsis due to bacteria such as *Escherichia coli*, *Enterococcus*, *Klebsiella*, methicillin-resistant *Staphylococcus aureus,* and *T pallidum*. Potential viral pathogens include enterovirus, echovirus, adenovirus, parvovirus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), human herpesvirus 6, and other viral hepatitides. Noninfectious possibilities include α_1-antitrypsin deficiency, hemophagocytic lymphohistiocytosis, and acetaminophen toxicity.

Treatment with vancomycin, cefotaxime, and acyclovir was initiated on hospital admission. Vitamin K, fresh frozen plasma, platelets, and packed red blood cells were administered. Acyclovir therapy was discontinued based on negative HSV polymerase chain reactions from mucosal, blood, and cerebrospinal fluid (CSF) samples. Results of CSF VDRL testing and plasma HIV RNA polymerase chain reaction were also negative. Three days later, liver dysfunction, anemia, and thrombocytopenia resolved. Antibiotic therapy was narrowed to ampicillin based on a blood culture with growth of *Enterococcus faecalis*. Syphilis was confirmed by serum *T pallidum* particle agglutination assay (TPPA) and rapid plasma reagin (RPR) titer (1:64). After the diagnosis of congenital syphilis, the infant received 10 days of intravenous aqueous penicillin G followed by 1 intramuscular dose of benzathine penicillin G. Both parents subsequently tested positive for syphilis (TPPA, RPR) and were treated. The infant was discharged after a normal ophthalmologic and audiology evaluation, with anticipation of periodic follow-up and serial nontreponemal antibody testing. The infant continues to be followed in the Pediatric Infectious Disease Clinic and had a greater than 4-fold reduction in RPR titer 3 months after hospital discharge (RPR titer of 1:8).

The Condition

This infant has congenital syphilis despite negative maternal first-trimester treponemal test results. Congenital syphilis is caused by transplacental transfer of *T pallidum*, a spirochete that is sensitive to penicillin. The incidence of congenital syphilis in the United States increased between 2012 and 2014. In 2014, there were 12 cases of congenital syphilis per 100,000 live births. (1) The incubation period of syphilis is typically 3 weeks but ranges from 10 to 90 days. (2) Risk factors for congenital syphilis include lack of prenatal care, substance abuse, sexual promiscuity, history of sexually transmitted infections, or contact with anyone with sexually transmitted infections. (3) Syphilis infection can occur throughout pregnancy and can result in miscarriage, stillbirth, prematurity, neonatal death, and congenital syphilis. (4)

The involvement of the placenta and subsequent hematogenous dissemination of *T pallidum* to the infant helps explain the multitude of clinical manifestations of congenital syphilis. Congenital syphilis is classified as early congenital syphilis, affecting infants from birth to 2 years old, and late congenital syphilis, affecting infants older than 2 years. Most infants with early congenital syphilis are asymptomatic at birth but can develop poor feeding, hepatomegaly, splenomegaly, jaundice, hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia, pneumonitis, nephrotic syndrome, rhinitis, maculopapular rash, generalized lymphadenopathy, fever, central nervous system dysfunction, and osteochondritis during the first few weeks after birth. (5) Manifestations of late congenital syphilis include interstitial keratitis, saddle nose, saber shins, Hutchinson teeth, eighth nerve deafness, mental delay, and convulsive disorders. (5) Concurrent bacterial sepsis, secondary to bacterial translocation across the gastrointestinal mucosal barrier, has also been reported. (6)

Diagnosis

Because *T pallidum* cannot be readily cultured, syphilis is typically diagnosed using a screening nontreponemal test followed by a confirmatory treponemal test. Nontreponemal testing includes the VDRL and RPR tests. Treponemal tests include TPPA, *T pallidum* enzyme immunoassay, *T pallidum* chemiluminescent assay, and fluorescent treponemal antibody absorption. A reactive nontreponemal test result needs to be confirmed by treponemal testing because the sensitivity of RPR and VDRL tests to detect primary syphilis is 86% and 78%, respectively. (7) The RPR test works by detecting lipoidal material released by cells that are infected with *T pallidum*. The RPR test results can become positive from treponemal infections as well as nontreponemal conditions. False-positives for nontreponemal tests occur in 1% to 2% of the US population and can be due to other infections, including hepatitis, varicella, measles, HIV, and mononucleosis; pneumonia; autoimmune disease; injection drug use; lymphoma; tuberculosis; malaria; and pregnancy. (8)(9) Because nontreponemal test results parallel disease activity, they are also used to monitor response to therapy. In congenital syphilis, the RPR and VDRL tests should show at least a 4-fold reduction in titer by the third month after treatment. (7) Fluorescent treponemal antibody absorption is the most commonly used treponemal confirmatory test, and it has sensitivity of 84% and specificity of 97% to detect primary syphilis. (7) Unlike nontreponemal tests, the titers from treponemal tests do not correlate with disease activity and cannot be used to monitor response to therapy.

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Treatment

The *Red Book* has recommendations, summarized herein, about the evaluation of infants who are born to mothers with a reactive serologic test for syphilis. (2) Mothers who have positive results of nontreponemal testing, such as RPR or VDRL, should receive a treponemal test. A negative treponemal test result strongly excludes the possibility of congenital syphilis. If a mother has a reactive treponemal test during the pregnancy, then evaluation of the infant is influenced by the mothers' treatment of syphilis.

If a mother who had syphilis was adequately treated with penicillin before the pregnancy, has either a low VDRL titer of 1:2 or less or a low RPR titer of 1:4 or less during the pregnancy, and the infant has normal examination findings, then the infant does not need an evaluation or treatment.

If the mother with syphilis was treated with penicillin more than 4 weeks before delivery and there is no evidence of maternal reinfection during the pregnancy based on maternal syphilis titers, then the infant should be tested for syphilis by RPR/VDRL testing. If the infant has abnormal physical examination findings and the infant's nontreponemal test is not 4-fold or greater than the mother's nontreponemal test, then the infant needs to be evaluated and treated for congenital syphilis. Infants who have 4-fold or greater nontreponemal titers also need to be evaluated and treated. Evaluation includes complete blood cell count, CSF examination for cell count, protein, glucose, and quantitative VDRL testing. Other tests should be ordered if clinically indicated, such as chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response.

Penicillin remains the drug of choice for the treatment of congenital syphilis. Treatment for congenital syphilis includes aqueous penicillin G 50,000 U/kg every 12 hours if 1 week of age or younger or every 8 hours if older than 1 week. Another option is procaine penicillin G 50,000 U/kg intramuscularly as a single daily dose for 10 days. If the infant's nontreponemal test is not 4-fold or greater than the mother's nontreponemenal test, then the infant can be treated with one single dose of benzathine penicillin G 50,000 U/kg intramuscularly if the infant has normal physical examination findings. These infants' nontreponemal titers should be followed monthly until the results are negative.

If a mother is not treated with penicillin for syphilis during the pregnancy, if the treatment is not documented, if the treatment occurred 4 weeks or less before the delivery, if a nonpenicillin drug was used, or if there is a 4-fold or greater increase in maternal syphilis titers, then the infant needs to be evaluated for congenital syphilis. If the infant's physical examination findings are normal, if the syphilis evaluation results are normal, and if the infant's nontreponemal titers are the same or less than 4-fold the maternal nontreponemal titers, then the infant should be treated with 10 days of penicillin G, either intravenously or intramuscularly, or with a single dose of benzathine penicillin G 50,000 U/kg intramuscularly. Most experts recommend 10 days of treatment. If the infant's physical examination findings are abnormal, if the evaluation results are abnormal, or if the infant's nontreponemal titer is at least 4-fold greater than the maternal nontreponemal titer, then the infant should be treated with 10 days of either aqueous or procaine penicillin. All infants with congenital syphilis should also be tested for other coinfections, including HIV, hepatitis B, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.

Infants with skin or mucus membrane lesions should be cared for with gloves until 24 hours of therapy has been completed because nasal secretions, blood, and discharge from lesions are potentially infectious. (6) A mother with syphilis may continue to breastfeed her infant as long as she does not have active lesions on her breast. There is no evidence that syphilis is transmitted through human milk among mothers without active breast lesions. (10) Laboratory follow-up after treatment includes VDRL/RPR testing every 3 months until the titer is negative or has decreased at least 4-fold.

Lessons for the Clinician

- A negative maternal first-trimester test for syphilis during pregnancy does not negate the risk of infants developing congenital syphilis.
- The Centers for Disease Control and Prevention (CDC) recommends that all pregnant women be tested for syphilis during the first trimester of pregnancy. Women at high risk for syphilis, including those who live in areas of high syphilis morbidity, who are previously untested, or who had a positive screening test result, should be screened for syphilis during the third trimester and at delivery. (11)
- The rise of congenital syphilis presents an opportunity for pediatricians and neonatologists to partner with obstetricians, family practitioners, internists, and public health departments about how to best screen for and prevent congenital syphilis.
- As long as syphilis continues to spread among adults, congenital syphilis will continue to pose a serious threat for infants.

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Case 6: Liver Failure and Rash in a 6-week-old Girl

Rishi Mediratta, Hayden Schwenk, Anoop Rao and Ritu Chitkara

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Acetaminophen Poisoning

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AUTHOR DISCLOSURE Drs Nadler and Fein have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Acetaminophen (*N*-acetyl-para-aminophenol) is one of the most prevalent medications on the market today, available for purchase in multiple different formulations: as an individual product (eg, Tylenol® [Johnson & Johnson Consumer Inc, Fort Washington, PA]), as a component in over-the-counter cold remedies (eg, DayQuil^{TM}/Nyquil^{TM} [Procter & Gamble, Cincinnati, OH], Alka-Seltzer Plus® [Bayer Corp, Whippany, NJ], and Dimetapp® Cold & Flu [Pfizer Inc, New York, NY]), and in combination with an opiate (eg, acetaminophen-codeine and Percocet® [Endo Pharmaceuticals Inc, Malvern, PA]). Being so widely available both over the counter and by prescription, it is a common cause of both accidental and intentional ingestions. As a class, analgesics (including acetaminophen) are the most commonly ingested medication, and in 2015, products containing acetaminophen were the reason for approximately 45,000 calls to poison control centers throughout the United States related to children.

Acetaminophen toxicity occurs via its metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), which ultimately leads to oxidative hepatic injury. In therapeutic doses, acetaminophen produces only minimal amounts of NAPQI because it is metabolized in hepatocytes via UDP-glucuronosyl transferase (UGT) and sulfotransferase (SULT) mainly to compounds that are readily excreted in the urine. In addition, any NAPQI that is produced is conjugated by glutathione into a nontoxic compound in the liver. However, with an overdose, the UGT and SULT metabolic pathways are saturated and glutathione stores become exhausted, resulting in free NAPQI and its oxidative injury to the liver.

Clinical signs and symptoms of acetaminophen toxicity can be thought of as occurring in 4 distinct stages: the first 24 hours (stage I); 24 to 72 hours (stage II); 72 to 96 hours (stage III); and 96 hours to 2 weeks (stage IV). During stage I, patients may be asymptomatic or may display gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain, and/or nonspecific systemic symptoms, such as pallor, diaphoresis, and malaise. Laboratory test results are typically normal at this time, although liver enzyme levels may rise as early as 12 hours after a massive ingestion. When the overdose is from acetaminophen alone, mental status typically is normal at first, although a massive overdose may result in a decreased level of consciousness or coma. In stage II, the initial symptoms typically resolve and evidence of hepatic injury, such as right upper quadrant pain and tenderness, develops. Elevation of liver enzyme levels occurs within 24 to 36 hours; other tests indicative of liver function, such as bilirubin and prothrombin time/international normalized ratio (INR), may begin to show evidence of abnormality. If the patient progresses to stage III, evidence of hepatotoxicity and liver failure ensues: there are massive elevations in transaminase levels, increased bilirubin levels, metabolic acidosis with an increased anion gap, and prolongation of the prothrombin time/INR; jaundice, hepatic encephalopathy, acute kidney injury (potentially hepatorenal syndrome or acute renal failure), and

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multi-organ failure can occur. Most deaths from acetaminophen toxicity occur during stage III. Stage IV is the recovery stage, where clinical symptoms resolve and laboratory abnormalities return to normal.

The diagnosis of acetaminophen toxicity is confirmed by obtaining a serum acetaminophen concentration. Toxicity may result from either an acute overdose or from repeated supratherapeutic ingestions of acetaminophen or acetaminophen-containing products. A single dose greater than 150 mg/kg in children and greater than 7.5 g in adults or supratherapeutic repeated doses amounting to greater than 200 mg/kg over 1 day or 150 mg/kg per day over 2 days is concerning for potential toxicity. Because acetaminophen is a common co-ingestant, a serum level should be obtained on all patients who present with any known or possible substance ingestion, even if acetaminophen is not explicitly mentioned. If possible, the level should be obtained 4 hours after an acute ingestion to best determine the risk of toxicity and assist with management. A level performed earlier may indicate acetaminophen ingestion but cannot accurately assess the risk of toxicity. When the time of ingestion is unknown, the earliest possible time that acetaminophen could have been taken should be used. For a long-term ingestion, a level should be drawn at the time of presentation. Liver and renal function tests should be drawn 8 to 10 hours after ingestion, although abnormalities often become evident only after 24 hours.

Management of acetaminophen toxicity begins with evaluation and stabilization of the patient's airway, breathing, and circulation. Activated charcoal may be useful if administered within 2 hours of ingestion, but it should be avoided in a patient with altered mental status, an unprotected airway, or co-ingestion with a corrosive or proconvulsant substance. The mainstay of treatment for acetaminophen toxicity is *N*-acetyl cysteine (NAC), which works by providing cysteine as a substrate to replenish hepatic glutathione stores and by shuttling unmetabolized acetaminophen to the SULT pathway, thereby halting production of NAPQI. Also, NAC may directly reduce NAPQI back to acetaminophen, preventing its hepatotoxic effect. The Rumack-Matthew nomogram (Fig) is a useful tool in guiding the management of an acute acetaminophen overdose when the time of ingestion is known and the patient presents within 24 hours. The acetaminophen level is plotted on the nomogram, and the decision whether to treat with NAC is determined accordingly. The treatment line starts at 4 hours after ingestion and decreases linearly over time. Although toxicity is probable at a serum concentration of 200 μg/mL, the treatment line was lowered to start at 150 μg/mL to increase the sensitivity of the nomogram. If the level is above the treatment line, NAC should be initiated. Ideally, treatment with NAC begins within 6 to 8 hours of ingestion, as its protective effect is dramatically higher when given within this period. If treatment will be delayed beyond this time or if the patient is symptomatic, NAC should be administered while the acetaminophen level is pending. The nomogram is not applicable when the time of ingestion is unknown, when the patient presents more than 24 hours after ingestion, and in long-term repeated exposures. In these situations, NAC should be started if the serum acetaminophen level is greater than 10 μg/mL or if transaminase levels are elevated.

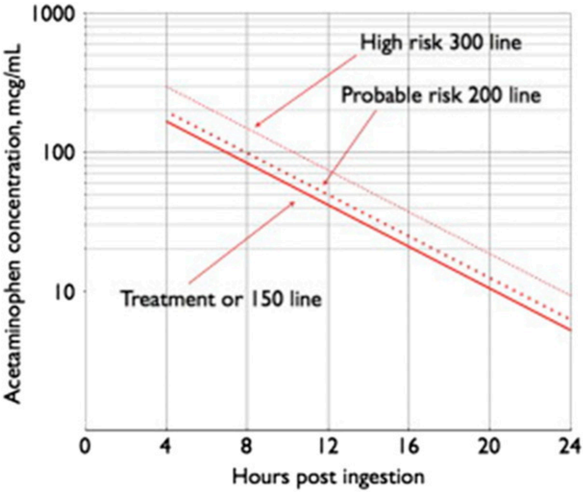

Figure. Rumack-Matthew nomogram.

Administration of NAC can be oral or intravenous. Both are equally effective in preventing and treating acetaminophen toxicity; however, intravenous NAC should be used preferentially for patients with fulminant hepatic failure, intractable vomiting, or pregnancy. Intravenous NAC is administered over 21 hours and has an associated risk of an anaphylactoid reaction, particularly during the initial loading dose and in patients with asthma. The oral form is given as a course of 18 doses over 72 hours. Aminotransferase levels, INR, and acetaminophen level should be determined before discontinuing NAC therapy. If laboratory abnormalities persist, NAC use should be continued until aminotransferase levels are improving, the INR has normalized, and the acetaminophen level is undetectable. In severely ill patients who progress to fulminant hepatic

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failure and do not respond to treatment with NAC, liver transplant may be lifesaving.

Anticipatory guidance at health-care maintenance visits is essential to prevent a toxic acetaminophen overdose. Parents should be advised to keep all products containing acetaminophen in locations inaccessible to children, strictly adhere to weight-based dosing, and avoid adult preparations and co-administration of acetaminophen-containing medications.

COMMENT: By far the most common reason for parents to give their children acetaminophen is to combat fever, but in many, if not most, instances this is a fight that is self-defeating. In contrast to the dangers of hyperthermia, fever is regulated by the hypothalamus as a homeostatic response to an inflammatory insult, and of itself almost never poses a threat to the febrile child. In fact, as a physiologic phenomenon fever has survived for millions of years among animals all along the spectrum from invertebrates to mammals, and given that fever comes at a metabolic cost in energy expended, evolution tells us it must have some survival benefit. Experimental evidence documents that fever can impede the growth of many pathogenic bacteria and viruses, although it enhances neutrophil migration, T-cell proliferation, and superoxide and interferon production. Yet our phobic response to fever, both as parents and as physicians, contributes to the more than 25 billion doses of acetaminophen sold in the United States each year, often given for fevers that are not discomforting or are not in fact fevers at all. Granted that most acetaminophen poisonings result from intentional overdosing, the frequency with which parents inadvertently give their children improper doses of medication makes the ubiquity of acetaminophen (and other antipyretics) a real concern.

– Henry M. Adam, MD
Associate Editor, *In Brief*

In Memoriam

The staff of Pediatrics in Review notes with sadness the passing of Sydney “Cindy” Sutherland, who for many years served faithfully and skillfully as an Editorial Assistant, working closely with Editors-in-Chief Robert Haggerty and Lawrence Nazarian. She is remembered for her exceptional command of the English language, her understanding of the goals of the journal, her passion for social justice, and her dynamic and delightful personality.

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Hemoptysis

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AUTHOR DISCLOSURE Drs Shnayder and Needleman have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Hemoptysis in children is rare but can be dramatic, frightening, and potentially life-threatening. The expectoration of blood or blood-tinged sputum presents the clinician with significant diagnostic and therapeutic challenges. An understanding of the etiology, diagnosis, and management of hemoptysis is important for all clinicians.

The blood supply to the lungs is composed of 2 circulatory systems, bronchial and pulmonary. The bronchial system is high pressure but low volume. Bronchial vessels arise from the aorta and its branches, supplying blood to the conducting airways, down to the terminal bronchioles. The pulmonary system is the opposite, low pressure and high volume. Vessels from this system arise from the right ventricle and supply the acini. Hemoptysis results when endothelial damage occurs, causing either low-volume bleeding if originating from the pulmonary circulatory system or profuse bleeding if occurring in the high-pressure bronchial system.

A variety of factors make it difficult to ascertain the incidence of hemoptysis in children: under the age of 6 years, children have a tendency to swallow their sputum; most cases are mild and resolve within 24 hours; and there is no mandatory reporting of most conditions that cause hemoptysis or pulmonary hemorrhage. Hemoptysis may result from a variety of causes (Table), ranging from the most common, such as infections, to more rare causes, such as vasculitides.

Evaluation of hemoptysis begins with establishing that the bleeding is from the lower respiratory tract and not from an extrapulmonary source, such as the gastrointestinal tract or the upper airway. Patients with hemoptysis may report a prodromal tingling in the throat or gurgling noise from the chest. If blood is coughed out, it is typically bright red, frothy, and may be mixed with sputum. Patients may note respiratory distress and can have a history of lung disease. In contrast, patients with hematemesis typically note abdominal pain and nausea, and the blood is vomited, usually brown or "coffee grounds" in color, and may be mixed with food particles.

In patients who appear critically ill with cardiorespiratory compromise, the priority is to stabilize the airway, breathing, and circulation. Then, the evaluation of hemoptysis begins with a thorough history and physical examination. Questioning should focus on a history of preexisting medical conditions, systemic symptoms, recent illness, and recent travel. A new, sudden-onset cough or wheeze can raise suspicion of foreign body aspiration. A history of hematuria can suggest a pulmonary-renal syndrome, and a history of calf pain raises concern for pulmonary embolus. The physical examination should include a thorough evaluation of the upper airway for sources of bleeding. A detailed pulmonary examination can help to localize the bleed or indicate the underlying cause. Cardiac auscultation may reveal a heart murmur, indicating a cardiac etiology. The skin examination is unlikely to demonstrate pallor but may uncover bruises or signs of trauma.

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TABLE. **Causes of Hemoptysis**

INFECTION	**VASCULAR ANOMALIES**
◦ Tracheobronchitis	◦ Pulmonary arteriovenous malformations
◦ Pneumonia (bacterial, viral, fungal, mycoplasma)	◦ Pulmonary embolism/thrombosis
◦ Tuberculosis	◦ Hemangioma
◦ Lung abscess	
BRONCHIECTASIS	**TUMOR**
◦ Cystic fibrosis	◦ Adenoid
◦ Ciliary dyskinesia	◦ Carcinoid
FOREIGN BODY ASPIRATION	**PULMONARY-RENAL VASCULITIDES**
TRAUMA	◦ Goodpasture syndrome
CARDIAC	◦ Henoch-Schonlein purpura
◦ Congenital heart disease	◦ Microscopic polyangiitis
◦ Pulmonary hypertension	◦ Systemic lupus erythematosus
CONGENITAL MALFORMATIONS	◦ Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
◦ Bronchogenic cyst	
◦ Congenital pulmonary airway malformation	
BLEEDING DISORDERS	**IDIOPATHIC PULMONARY HEMOSIDEROSIS**
◦ Disseminated intravascular coagulation	**DRUG TOXICITY**
◦ Thrombocytopenia	**FACTITIOUS HEMOPTYSIS**

In continuing the evaluation, a complete blood cell (CBC) count, coagulation profile, inflammatory markers (C-reactive protein and erythrocyte sediment rate), and urinalysis should be sent. A CBC count can help quantify the amount of blood lost. Derangement in the coagulation profile can indicate an underlying coagulopathy. Inflammatory markers can suggest inflammation in the setting of infection or vasculitic disease. Proteinuria or hematuria may point to a pulmonary-renal syndrome and require further laboratory studies. Because infection is the most common cause of hemoptysis, sputum from expectoration, nasotracheal suction, or bronchoscopy should be sent to the laboratory to help distinguish among bacterial, fungal, and mycobacterial infections and tailor treatment accordingly.

The plain chest radiograph can be useful. Most commonly it can demonstrate focal or diffuse opacities consistent with infection. Other potential findings include hyperinflation suggestive of a foreign body, atelectasis, interstitial infiltrates, pleural effusion, cardiomegaly, and the typical tram-track sign suggestive of bronchiectasis. In 33% to 50% of patients, results of chest radiographs are normal, and patients require further imaging to better assess the origin of their hemoptysis. Computed tomographic (CT) scanning with contrast angiography can be an important tool in depicting and localizing the underlying cause, including a vascular abnormality, infection, or bronchiectasis. On CT scan, an acute bleed manifests as a focal consolidation with surrounding areas of ground glass appearance. Further studies can include magnetic resonance imaging or echocardiography to investigate possible cardiac causes.

Bronchoscopy is indicated if the source of the blood remains unknown and bleeding persists. Flexible bronchoscopy allows for better visualization of the distal bronchial tree and can be used to take cytologic, histiopathologic, and microbiologic specimens. In clinical scenarios where a foreign body is suspected, a patient has heavy bleeding, or

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there is the potential for respiratory compromise, rigid bronchoscopy is the preferred modality: it allows for the removal of foreign bodies, suctioning of blood, and injection of hemostatic agents while providing effective ventilation and airway stability.

The treatment of hemoptysis depends on the underlying cause and the severity of the bleed. In pediatrics, most episodes of hemoptysis are mild and resolve spontaneously without invasive treatment. In children who are clinically stable and the specific etiology of their hemoptysis is suspected, management is directed at the underlying cause. In situations of massive bleeding, rigid bronchoscopy is indicated so that topical vasoconstrictors can be applied to curtail the bleeding and, if needed, endobronchial tamponade can be performed.

In rare cases, when bleeding persists, the responsible blood vessel needs to be embolized: bronchial arteriography is performed to identify the bleeding vessel, and, once identified, the vessel is then cannulated and embolized using an absorbable gel sponge, a coil, or polyvinyl alcohol particles. In 77% of cases, embolization results in immediate cessation of bleeding, as well as long-term control beyond 3 months in 45% of all cases.

COMMENT: Drs Shnayder and Needleman mention that young children tend to swallow their sputum, the inference being that some cases of what really is hemoptysis go unrecognized. When bloody sputum from a hemorrhage in the lungs is swallowed, it can be a gastric irritant leading to vomiting; and the bloody vomitus can easily be misdiagnosed as hematemesis. Although both hemoptysis and hematemesis can be life-threatening, while the alarm bells go off it can be calming to remember that in children, both conditions, frightening as they are, most often are relatively benign and self-limited.

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR JUNE 2018 PEDIATRICS IN REVIEW

Burn Care for Children: 1. B; 2. A; 3. D; 4. B; 5. B.
Staphylococcus aureus: 1. A; 2. E; 3. D; 4. B; 5. C.
Intellectual Disabilities: 1. B; 2. B; 3. D; 4. D; 5. C.

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Hemoptysis

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Visual Diagnosis

Syncopal Episode in a 14-year-old Adolescent Boy

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PRESENTATION

A 14-year-old Hispanic boy with a medical history significant for panic attacks and depression presents to the emergency department after a syncopal episode. He was in school at the time of the event, and the last thing he remembers before losing consciousness is that he was sitting on the edge of the school theater stage. The event was witnessed by his schoolmates, who alerted their teachers. He woke up spontaneously but appeared confused. Emergency medical services were notified, and he was taken to the emergency department.

Before this episode, he had no history of headache or dizziness. He has had chest pain and palpitations previously, but he attributes these symptoms to the panic attacks. He was in his normal state of health and has never experienced a syncopal episode until this time. He does not engage in sports at school but is able to participate in regular physical activity without experiencing difficulty or limitation of activity. Of note, the boy has experienced several panic attacks over his lifetime, with the most recent being 1 year ago. He denies any associated syncopal events. His social history is significant for admission to a psychiatric hospital due to suicidal ideation several months before this presentation. Currently, he is taking fluoxetine and aripiprazole but does not use alcohol or other substances. The family history is normal.

On evaluation in the emergency department, he is afebrile, with a heart rate of 99 beats/min, respiratory rate of 12 breaths/min, and blood pressure of 124/70 mm Hg. The initial evaluation shows normal electrolyte values and complete blood cell counts. In addition, his troponin level is 0.0 ng/mL (0.0 μg/L) (reference range, 0.00–0.045 ng/mL [0.00–0.045 μg/L]).

An electrocardiogram (ECG) is obtained and shows J-point elevation with inverted T waves in V_1 and V_2 (Fig 1). He is transferred for cardiac evaluation and management. On admission, his physical examination, weight, height, and body mass index are appropriate for age. The patient appears calm and comfortable and responds to questions appropriately. The remainder of his physical examination findings are normal.

DIAGNOSIS

An ECG is repeated to confirm the initial ECG findings and shows persistence of J-point elevation with inverted T waves in V_1 and V_2 (Fig 1). A transthoracic

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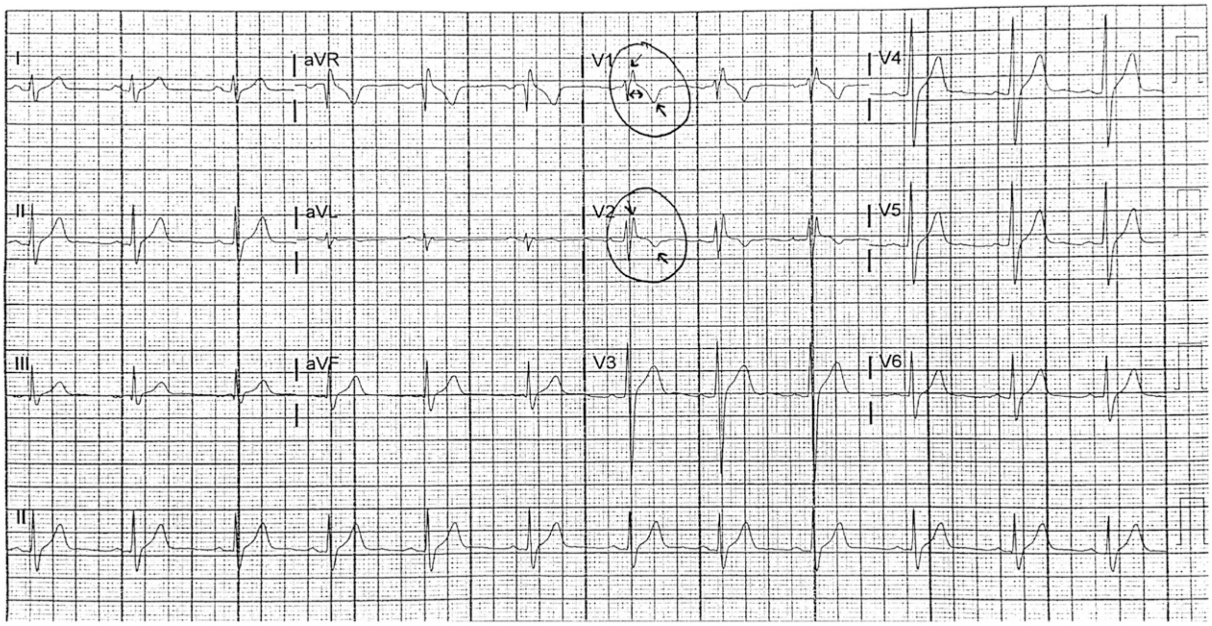

Figure 1. Circled regions demonstrate Brugada pattern with a coved ST-segment elevation after inverted T waves in precordial leads V_1 and V_2.

echocardiogram does not reveal any structural heart disease. The cardiac electrophysiology service is consulted and confirms Brugada pattern, likely type 1. Before intervention, an electrophysiology study is performed, including a procainamide challenge. Again, Brugada type 1 ECG pattern is confirmed. Hemodynamically unstable ventricular tachycardia is induced with isoproterenol infusion and resolves after synchronized electrical cardioversion. In light of these findings, a single-chamber implantable cardiac defibrillator is placed.

DISCUSSION

Brugada syndrome, first described by Drs Pedro and Josep Brugada in 1992, (1) is a channelopathy characterized by syncope or sudden cardiac death with typical ECG findings in young people without structural heart disease. (1)(2) Symptoms are caused by ventricular arrhythmias such as ventricular fibrillation and ventricular tachycardia. (3) There are 3 subsets of Brugada ECG pattern known. A coved-type ST-segment elevation ($\geq$0.2 mm) present in at least 1 of the right precordial leads (V_1–V_3) with an inverted T wave is a diagnostic finding for type 1 morphology (Fig 2). (2)(3)(4) In types 2 and 3, a saddleback pattern is seen but is only suggestive of diagnosis, and further testing is indicated (Fig 2). (3)(4) If the initial ECG is nondiagnostic, further testing with procainamide or other sodium channel blockers can be performed to confirm type 1 disease. (2)(3) In 2013, a consensus report for electrographic criteria for diagnosis of Brugada syndrome was published. (5)

The inheritance pattern for Brugada syndrome is autosomal dominant with variable penetrance. (2) Implicated genes involved are *SCN5A* and *SCN10A,* but others have been described. (3)(5)(6) Mutation in these genes causes an impairment of the myocardium sodium channels, causing a reduced sodium inflow current, which leads to a decrease in the duration of the normal action potential and, therefore, an increased risk of ventricular tachyarrhythmias. (6)

Patients who are diagnosed as having Brugada syndrome often present with a cardiac event, such as sudden cardiac arrest, unexplained syncope, or tachyarrhythmias without evidence of structural heart disease. (3) These events tend to develop during rest or sleep (2) and rarely occur with exercise. (3) The Brugada pattern has been defined as characteristic ECG findings of Brugada syndrome without symptoms. The Brugada ECG pattern has been found to occur spontaneously, meaning that there are ECG changes without any inciting factors, or can be induced by fever, electrolyte abnormalities (hyperkalemia, hypokalemia, hypercalcemia), alcohol, cocaine, and drugs such as sodium channel blockers, α-agonists, β-blockers, and selective serotonin reuptake inhibitors. (2)

For diagnostic purposes, a patient is diagnosed as having Brugada syndrome with type 1 morphology when ST-segment elevation (>1 mm) is seen in right precordial leads V_1 and V_2. (5) Brugada syndrome is also definitively diagnosed when an ECG showing types 2 and 3 morphology (saddleback appearance) converts to type 1 with administration of a sodium channel blocker (5) with or without superior lead placement.

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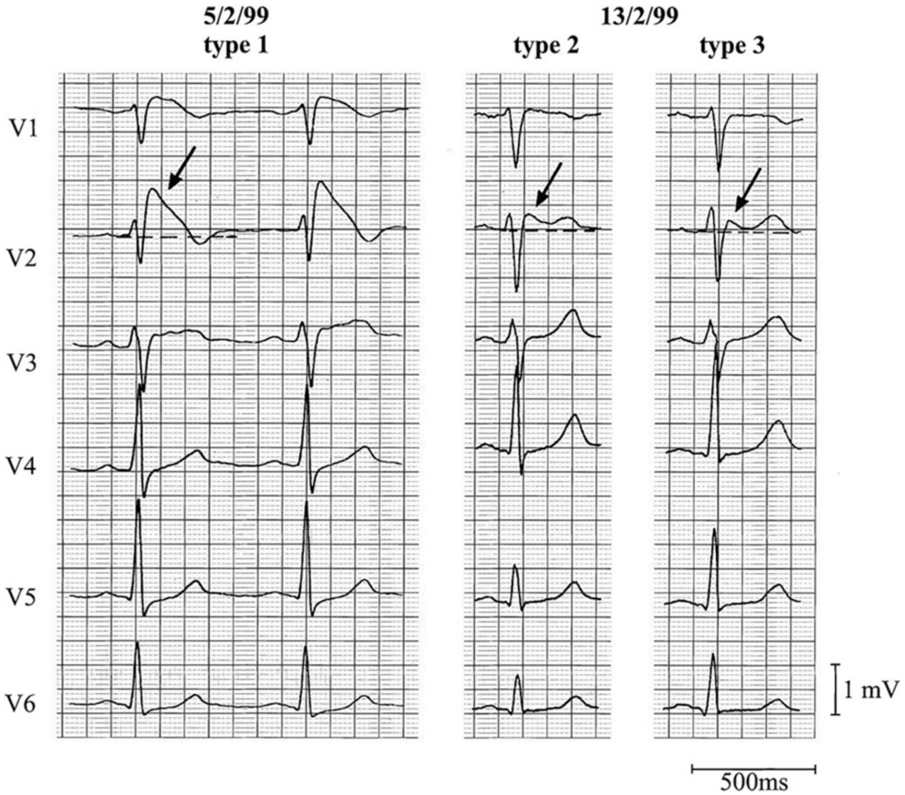

Figure 2. Type 1 has a coved-type ST-segment elevation in at least 1 of the right precordial leads (V_1–V_3) with inverted T waves. Types 2 and 3 have a saddleback pattern but are only suggestive of diagnosis, and further testing is indicated. (Adapted from Wilde AA, Antzelevitch C, Borggrefe M, et al; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002:106(19):2514–2519).

Differential Diagnosis

The differential diagnosis of syncope in an adolescent can be wide. Benign causes include orthostatic hypotension due to dehydration, vasovagal syncope, and symptomatic anemia. Life-threatening causes include cerebrovascular accident, structural heart disease, acute coronary syndrome, bradyarrhythmias, and tachyarrhythmias. Other considerations should also include medication or substance use and dysautonomia.

Brugada syndrome is primarily seen in adults in the fourth and fifth decades of life, and 70% to 90% of cases are in men. (3) The syndrome is rarely seen in children, (3) and the diagnosis requires a trained physician to recognize the ECG findings associated with it. The prevalence is low, estimated to be 0% to 0.3%, and is contingent on the population studied. (3) Prevalence is greater in individuals of Asian descent, particularly southeast Asia. (3)(5)(6)

Management

Current recommendations endorse implantable cardioverter defibrillator (ICD) placement in adult patients with spontaneous type 1 ECG pattern who are also symptomatic because they are at highest risk for recurrent cardiac events. (3)(7) A similar recommendation was also made in a study involving patients younger than 19 years. (8) Although more studies are needed, asymptomatic patients with spontaneous type 1 Brugada pattern or those with drug-induced Brugada pattern are presently deemed low risk for developing malignant tachyarrhythmias, and ICD therapy is not indicated. (7)(8) Our patient was taking fluoxetine before the event. Animal data suggest that fluoxetine may cause drug-induced Brugada syndrome, but there are no reports of this association in humans. (9) Other recommendations include avoidance of possible triggers such as medications and alcohol, and use of antipyretics for fever. Pharmacologic therapy with use of medications such as quinidine can be considered for high-risk patients as an adjunct therapy to ICD or by itself due to patient preference or an existing contraindication with ICD placement. (3)

Prognosis

During the early discovery of the syndrome and subsequent follow-up studies, the prognosis of Brugada syndrome was ominous. (3)(10) Twenty-seven percent of asymptomatic patients had a cardiac event within the 34 months of follow-up, and, consequently, the widespread use of prophylactic ICD was recommended. (3)(10) However, in the past decade, a variety of published studies actually demonstrate that the risk of cardiac events is relatively low in patients with Brugada ECG findings, particularly in those who are

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asymptomatic or have a drug-induced type 1 pattern. (7) Those who have had a cardiac event are at 48% risk within 10 years of having another episode compared with 0.5% to 1.5% per year risk for those who are asymptomatic. (3)

Patient Course

After positive procainamide and isoproterenol challenge tests, an ICD was placed. He tolerated the procedure well and was discharged from the hospital the next day without complications. He has followed up in the cardiology clinic at 2 weeks, 6 weeks, and 3 months after hospital discharge and has done well. Genetic testing was also ordered for the family, and the results are pending.

Summary

- Brugada syndrome should be included in the differential diagnosis for children who present with unexplained syncope. The ability to recognize the characteristic electrocardiographic (ECG) findings is an important first step in making this diagnosis.
- Brugada syndrome is definitively diagnosed when a type 1 ECG, coved-shaped pattern is associated with symptoms. Brugada syndrome is also definitively diagnosed when a type 2 or 3, saddleback pattern converts to type 1 with the use of sodium channel blockers or with superior lead placement. This has to be accompanied by clinical symptoms.
- Symptomatic patients with Brugada ECG patterns are at high risk for recurrent cardiac events, and implantable cardioverter defibrillator implantation should be considered.
- Asymptomatic patients without risk factors for cardiac events (ie, patients with a Brugada pattern on ECG) remain at low risk for future cardiac events.

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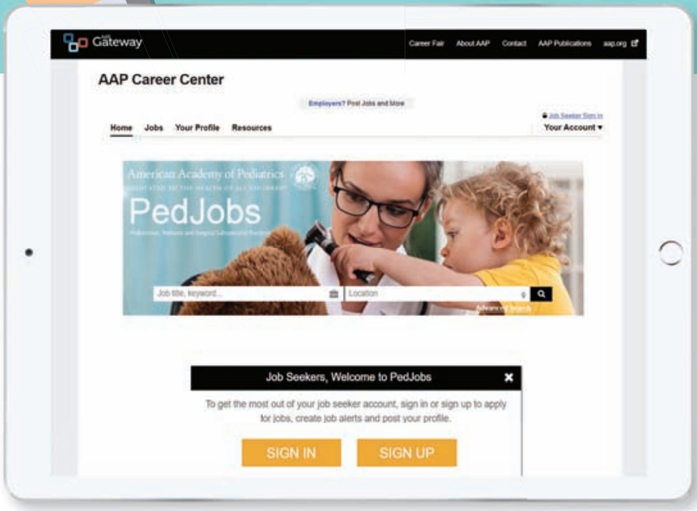

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BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

- BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO
- Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals
- Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope
- The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%)
- Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains
- Vaccination with BEXSERO may not result in protection in all vaccine recipients

Please see accompanying brief summary of full Prescribing Information for BEXSERO.

References: 1. Prescribing Information for BEXSERO. **2.** Prescribing Information for TRUMENBA.

BEXSERO is a registered trademark of the GSK group of companies.

BRIEF SUMMARY

BEXSERO® (Meningococcal Group B Vaccine)
Suspension for intramuscular injection

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO® is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. *[see Description (11) of full prescribing information]*

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of vaccine effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1) of full prescribing information].*

5.5 Altered Immunocompetence

Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In four clinical trials, 3058 individuals 10 through 25 years of age received at least one dose of BEXSERO, 1436 participants received only BEXSERO, 2089 received only placebo or a control vaccine, and 1622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in US and Poland, 120 participants 10 through 25 years of age received at least one dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by Menveo [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49% and 60% were White; 34% were Hispanic, 4% were Black,<1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) 11 through 17 years of age received at least one dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (UK), 974 university students 18 through 24 years of age received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1 dose of Menveo followed by 1 dose of placebo containing aluminum hydroxide (N=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (N=947). Across groups, median age was 20 years, males comprised 46%, and 88% were White, 5% were Asian, 2% were Black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were White, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, US/Poland, Canada/Australia, and in a subset of participants in the UK study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the US/Poland study, reports of unsolicited adverse events were collected up to one month after the second vaccination. Reports of all serious adverse events, medically attended adverse events and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), UK (12 months), US/Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants 10 through 25 years of age following each dose of BEXSERO administered 2 months apart or control in the US/Polish study[1] are presented in Table 1.

Table 1: Percentage of US and Polish Participants 10 through 25 Years of Age Reporting Solicited Local and Systemic Adverse Reactions within 7 Days after BEXSERO or Control, by Dose

Solicited Reaction[a]		Dose 1		Dose 2[b]	
		BEXSERO	Placebo (Saline)	BEXSERO	Menveo
		N=110-114	N= 94-96	N=107-109	N=90-92
Local Adverse Reactions					
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	> 50-100 mm	1	1	2	4
	> 100 mm	0	0	0	2
Systemic Adverse Reactions					
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

Clinicaltrials.gov Identifier NCT01272180.

[a] Erythema, and induration: Any (≥ 1 mm). Pain and systemic reactions: mild (transient with no limitation in normal daily activity); moderate (some limitation in normal daily activity); severe (unable to perform normal daily activity)

[b] Administered 2 months after Dose 1

Solicited adverse reaction rates were similar among participants 11 through 24 years of age who received BEXSERO in the other three clinical studies,[2,3,4] except for severe myalgia which was reported by 3-7% of subjects. Severe pain was reported by 8% of university students in the UK[3].

(continued on next page)

Non-serious Adverse Events

In the 3 controlled studies[1,2,3] (BEXSERO N=2221, control N=2204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) BEXSERO and 197 (9%) control recipients. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in BEXSERO recipients than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants 10 through 25 years of age who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO N=2716, Control N=2078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) BEXSERO recipients and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at two universities in the US, BEXSERO was administered as a 2 dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals 16 through 65 years of age who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one event considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

Adverse event reports received for BEXSERO marketed outside the US are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency, or to establish a causal relationship to vaccination. This list includes serious events or events which have suspected causal association to BEXSERO.

General disorders and administration site conditions:	Blisters at or around the injection site.
Immune System Disorders:	Allergic reactions (including anaphylactic reactions), rash, eye swelling.
Nervous System Disorders:	Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility in females or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Pregnancy Registry for BEXSERO

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to BEXSERO during pregnancy. Women who receive BEXSERO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years of age.

15 REFERENCES

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2. NCT00661713 (V72P10)
3. NCT01214850 (V72_29)
4. NCT01423084 (V72_41)
5. Wang X, et al. *Vaccine.* 2011; 29:4739-4744.
6. Hosking J, et al. *Clin Vaccine Immunol.* 2007;14:1393-1399.

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling.*

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gsk GlaxoSmithKline

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Genetic Counseling in Pediatrics

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Education Gap

Physicians should be aware that genetic counselors can serve as a trusted resource for both physicians themselves as well as their patients and families. Genetic counselors are skilled in the areas of health-care communication, patient education, risk analysis, the genetic testing process, and family support.

Objectives

After completing this article, readers should be able to:

1. Discover the role of a genetic counselor in a pediatric setting.
2. Recognize circumstances in which genetic testing may be beneficial.
3. Differentiate the roles and training backgrounds of medical geneticists and genetic counselors.
4. Understand when to refer a patient to a geneticist or genetic counselor.

Abstract

Genetic counseling is a communication process whereby an individual or family obtains information about a genetic condition, is helped to understand the implications and significance of the condition, and is given resources to help with coping and management. It is a continuous process involving lasting supportive relationships between the family and the genetic professional. Genetic counselors are master's level–trained health-care professionals who work closely with pediatricians and pediatric subspecialists alike. Genetic counselors can be a source of information about genetic conditions, risk assessment for disease, and genetic testing. Although most of a genetic counselor's job is patient care and education, genetic counselors also serve as resources to educate health professionals about genetics.

AUTHOR DISCLOSURE Mr Stein and Mss Loman and Zuck have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

INTRODUCTION

A 3-year-old boy was born with a cleft palate that was successfully repaired at 1 year of age. He has been generally healthy since but has yet to develop expressive speech. His parents and older siblings are in good health with normal intellect. Could the cleft palate and lack of expressive speech be related? How could one find out? Is there a genetic test that should be performed? What is the impact to family members if a genetic diagnosis is made? How could genetic counseling benefit the family?

In cases such as this, a genetics consultation, involving the team of a geneticist and a genetic counselor, is an appropriate next step given the cleft palate and lack of speech. Together, with the family, they can decide whether genetic testing is medically indicated and if so, which type. If genetic testing is pursued and the results are informative for making a diagnosis, tailored genetic counseling, including education, resources, and psychosocial support, can be provided to the family.

Genetic counselors are a part of health-care teams and provide information to patients in a variety of different settings and specialties. Pediatrics is one of the most common areas of clinical practice for a genetic counselor and is a focus of this article.

GENETICS, GENETIC COUNSELING, AND PEDIATRIC GENETIC COUNSELORS

Genetic counselors are integrated into the pediatric setting by providing direct patient care (ie, meeting face-to-face with families) and by serving as a reliable resource to pediatricians, nurses, administrators, and other members of the health-care team. Historically and currently, the most common setting for the pediatric genetic counselor has been working alongside a medical geneticist in a medical genetics clinic. This setting, however, is evolving and some genetic counselors now work as closely with other pediatric providers, such as neonatologists, neurologists, pulmonologists, cardiologists, oncologists, or developmental pediatricians—all of whom see patients with genetic conditions in their practice and/or are involved in ordering genetic testing (Table 1). No matter the setting or the scenario, a variety of core components are typically included in the genetic counseling process, including family and medical history interpretation, patient education, psychosocial assessment, and facilitated decision making.

TABLE 1. **Examples of Genetic Conditions, by Pediatric Subspecialty, that Warrant the Involvement of a Genetic Counselor**

PEDIATRIC SUBSPECIALTY	SAMPLE GENETIC CONDITIONS WARRANTING GENETIC COUNSELING
Cardiology	Long QT syndrome Marfan syndrome
Dermatology	Ichthyosis Tuberous sclerosis
Developmental-behavioral	Fragile X syndrome Rett syndrome
Endocrinology	SHOX deficiency disorders Turner syndrome
Gastroenterology	Alagille syndrome Turner syndrome
Hematology	Sickle cell disease Hemophilia
Immunology	Chronic granulomatous Severe combined immunodeficiency
Nephrology	Alport syndrome Nephrogenic diabetes insipidus
Neurology	Friedreich ataxia Muscular dystrophy
Oncology	Li-Fraumeni syndrome von Hippel-Lindau syndrome
Ophthalmology	Leber congenital amaurosis Retinitis pigmentosa
Otolaryngology	22q11.2 deletion syndrome Usher syndrome
Pulmonology	Cystic fibrosis Primary ciliary dyskinesia
Rheumatology	Ankylosing spondylitis Ehlers-Danlos syndrome

Medical and Family Histories

One core aspect of genetic counseling, *information gathering*, is most commonly performed as the collection of family and medical histories. Genetic counselors typically obtain detailed family histories that involve eliciting and creating a 3-generation pedigree, which is subsequently added to the medical record. The eliciting of the pedigree includes obtaining general health information on family members as well as asking targeted questions specific to the referral indication. For example, if a patient were to be referred for an indication of multiple café-au-lait macules with concern for neurofibromatosis type 1 (NF1), then the eliciting of the family history should include targeted questions about other family members' potential features of NF1 as well as similar genetic conditions. In this situation, a genetic counselor will ask whether family members have café-au-lait macules or "birthmarks" similar to the patient; if there is a family history of any tumors, "lumps or bumps" of any sort; if there is any freckling in the groin or arm pits of any family members; or if learning disabilities are present in the family because these can all be characteristics associated with NF1. The genetic counselor will also ask about family history of hearing loss or ringing in the ears because these can be features of NF2, a similar condition. Once a detailed family history is obtained, it is assessed, analyzed, and interpreted to aid in determination of the likelihood of a genetic condition in the patient, the most likely inheritance pattern, and the chances of recurrence for family members. Medical history is interpreted in the context of family history to help assess the likelihood of a genetic diagnosis. For those with an established diagnosis, family history information is used to help determine chances of recurrence. This includes risk calculation, risk assessment, and sometimes Bayesian analysis to determine the chances of family members or any future offspring being affected with the same condition.

Family history and medical information are also used to help determine the necessity of genetic testing for both the patient and family members. If other family members have previously had genetic testing for a specified condition, this information is essential in determining the appropriate testing for a patient for that condition. For example, with NF1, if the proband (ie, the person serving as the starting point for the genetic study) has had full sequencing of the *NF1* gene, then the pedigree can be used to determine which family members may benefit from targeted variant testing and for whom genetic testing would be contraindicated based on inheritance. This is significant given that there is great variability and expense associated with genetic testing.

Patient Education

Individuals or families with a genetic condition (or at risk for a genetic condition) commonly seek information about the diagnosis itself, prognosis, management, and implications to the family, thus making education an essential and multifaceted element of genetic counseling. It involves talking with families about inheritance patterns, helping families to understand how this information may impact them, and what it all means for their family. Patient education also involves teaching families about genetic conditions, their features, long-term prognosis, and management/treatment options. Even before a diagnosis, families are educated about any genetic testing that may be recommended for the patient. This includes a variety of aspects such as the name of the test, what it will test for, what it will not test for, limitations of the test, and the possible results of the test.

In the genetic counseling setting, the genetic counselor will often have a preplanned outline of topics considered essential to cover. Depending on the referral indication, this outline may include the condition name, symptoms, prognosis, diagnostic tools, formal genetics, genetic testing, recurrence risks, and/or inheritance patterns. For any educational topic, visual aids are crucial in a genetic counseling session to help orient people's attention as well as helping with patient understanding. This is especially true with numbers and probabilistic information. (1) Pictures, charts, and other visuals are a way to help translate complex genetic topics into something patients and their families can better understand. Similarly, genetic counselors will often also try to use analogies to help families better understand genetic concepts. When discussing inheritance patterns, the pedigree itself can be used as a visual aid.

At its core, genetic counseling is built on the essential tenet of effective communication, that is, communicating complex information with clarity in both the oral and written forms. To that end, genetic counselors regularly provide families with written information and resources. Because genetic topics can be immensely complex, summary letters or "patient letters" are sometimes sent to families after an appointment with a genetic counselor. These letters provide families with a summary of the pertinent information that was discussed at the visit and can serve as a resource to be referred back to later or shared with other family members. (2)

Genetic counseling itself is not necessarily confined to a single visit. At an initial appointment, a genetic counselor may only briefly discuss the suspected condition but then go into more detail once an official diagnosis is established. The initial shock of a new diagnosis may make it difficult for a family to fully comprehend the information in a single visit. Furthermore, the very nature of the profession also means that sometimes genetic counselors must deliver upsetting or bad news. This news may sometimes be better absorbed in multiple steps.

For some individuals, genetic counseling occurs across the lifespan. A prime example is individuals/families with metabolic conditions diagnosed by newborn screening. Initially, the educational components focus on the parents and their needs. Over time, the child may become a more active participant in his or her own health-care and wonder why he or she has to attend medical visits or eat foods different from their friends. Pediatric genetic counselors are trained in translating difficult genetic concepts into explanations that parents and children of varying educational levels and different developmental stages can understand.

Psychosocial

Helping a family cope with a genetic diagnosis or with the continuing uncertainty of searching for one can be challenging. Because of this, an understanding of the psychosocial consequences of a genetic diagnosis is important to provide appropriate assistance. Fear and worry are common feelings of parents of children with genetic diagnoses, as are guilt, shame, and uncertainty. Genetic counselors are trained to work with families who may be feeling this way. Listening and support are crucial to understand how a patient or a family member is feeling and to better understand the impact that a genetic condition is having on the patient/family. Genetic counselors provide families with a space to share their experiences and the impact that a genetic diagnosis, or lack of, has had on their life and work. They also help connect families with support groups, similarly affected families, and other community or national resources. In addition, they advocate on behalf of the patient in arenas such as the health and educational systems.

Patient Decision Making and Informed Consent

It is worth noting that when it comes to making decisions regarding genetic testing, family planning, or medical procedures, a genetic counselor does not direct or influence the patient on what decision to make but rather presents information in a nonjudgmental fashion—not with the purpose of encouraging or discouraging a particular course or action. In the era of precision medicine, precision consent is also necessary. In other words, genetic counselors are trained (and strive) to help patients/families make decisions that are right for them. In the pediatric setting, this often involves helping families decide whether a certain genetic test is something they would like to pursue. There are many factors that a family can consider when deciding if they want to undergo genetic testing, including the possible results of the test, how the results could change management, what undesirable information they could learn from the test, the impact of a positive or a negative result, whether having a confirmed diagnosis is important to them, how much the test costs, and whether the test will be covered by insurance. Patients/families must consent to genetic testing before it begins, and this consent should be voluntary and rooted in patient understanding of the many variables.

Genesurance Counseling

A more recent addition to the roles and responsibilities of genetic counselors centers around genesurance counseling. Genesurance counseling is that portion of a genetic counseling session, whether intentional or unintentional, that is devoted to the topic of costs and insurance/third-party coverage (particularly for genetic testing). (3) Genesurance counseling helps to educate families about the financial aspects of a genetic test, which is often an important factor for families when deciding whether they would like to pursue genetic testing. Through genesurance counseling, genetic counselors help families understand the financial aspects of any recommended genetic testing, including medical necessity, deductibles, list price, and pricing differences among laboratories. In many cases, prior authorization for a genetic test may be needed, or there may be additional steps required to determine whether a genetic test will be a covered service. Genetic counselors have found themselves helping to navigate this process for patients and their families in recent years. In addition, many families have questions surrounding release of genetic test information to third-party payers, insurability after a genetic diagnosis, potential genetic discrimination, and confidentiality. It is important for genetic counselors to stay current on the ethical, legal, and social implications of genetic testing so that they may provide the most relevant and timely information in this regard.

THE COMPLEXITIES AND NUANCES OF GENETIC TESTING

Knowing when to order a genetic test and choosing the right genetic test takes an in-depth knowledge of the nuances, functionality, and capabilities of the test. Similarly, it is necessary to know under which circumstances genetic testing may or may not be indicated.

There are several reasons why genetic testing is beneficial in the right circumstance. A primary reason is that making or confirming a diagnosis can lead directly to changes in medical management. For example, depending on the genetic condition this could mean additional hearing, vision, musculoskeletal, or heart screening. Or, it could mean eligibility for a clinical trial, treatment, or therapy. In addition, making a genetic diagnosis often helps with prognosis. Although each patient is uniquely different despite his or her diagnosis, typically a positive/informative genetic test gives some insight about what to expect for a child's future.

In some cases, genetic testing allows families to end a diagnostic odyssey, thereby giving a name to their condition previously only broadly describable by a collection of symptoms. Although some may argue that ending a diagnostic odyssey is not an extrinsically purposeful reason to pursue genetic testing because it does not change medical management, it does ultimately end up saving the family's time and financial resources. (4) In addition, families who ultimately receive a diagnosis for their child often use this information to connect with other families. Although genetic diseases are collectively common, they are individually rare, meaning that there may be no other families in the region similarly affected. Social media, however, has made it possible for families from across the country or around the world to connect and share advice and resources, and in some cases, arrange meetings in a central location.

Advances in the robustness of genetic testing, such as exome sequencing in which thousands of genes are screened simultaneously, have made ending the diagnostic odyssey more commonplace in recent years. This type of genetic testing is expensive, however, costing thousands of dollars (Table 2). Although exome testing is appropriate in some limited circumstances, in other cases a different type of testing, such as a single-gene test, a panel test involving multiple genes, carrier testing, or site-specific testing for a known familial mutation may be the best option. Although describing the differences in these test options is beyond the scope of this article, it is important to know that each test carries with it extreme differences in pricing, robustness, accuracy, and sensitivity. Genetic counselors (and medical geneticists) are trained in determining the most appropriate approaches to genetic testing as well as in the interpretation of the positive, negative, or uncertain results that follow.

A confirmed or new diagnosis, based on genetic testing, will allow recurrence risk to be determined and may impact the family in several ways. If the condition is a sporadic event caused by a new spontaneous gene mutation (de novo mutation), the recurrence risk is low to the family. On the other hand, if the condition is deemed to be autosomal recessive, the parents then have a 1 in 4 risk with any given pregnancy to have an additional affected child and, depending on the seriousness of the condition, may want to weigh several reproductive options. These options could include deciding not to have any more children, using a donor egg, donor sperm, adoption, prenatal diagnosis, or preimplantation genetic diagnosis, which allows couples to have their own biological children and avoid prenatal diagnosis by testing embryos created by in vitro fertilization before implantation.

TABLE 2. **Relative Costs of Commonly Ordered Genetic Tests**

TYPE OF GENETIC TEST	RELATIVE COST
Targeted testing for a known familial variant	$
FISH for single chromosome location	$
Chromosome analysis/ karyotype	$$
Chromosomal microarray	$$$
Single-gene testing	$$–$$$$$$
Genetic testing panel of multiple genes	$$$–$$$$$$$$$$$$
Exome sequencing	$$$$$$$$$$–$$$$$$$$$$$$$$$$$$$$$

The cost of genetic testing varies greatly between different performing laboratories, but, in general, targeted testing for a single known familial variant is on the least expensive end of the spectrum, with exome sequencing on the more expensive end. For illustrative purposes only, each "$" in the table could be thought of as representing approximately $500 (based on market analysis and expert opinion). FISH=fluorescence in situ hybridization.

Despite compelling reasons to consider genetic testing in appropriate circumstances, there are equally as compelling reasons to avoid genetic testing for some patients and conditions, including conditions with no symptoms until adulthood or no pediatric preventive care options. One such situation is when a condition will not display symptoms until adulthood or there is no cure or screening recommendations in childhood. Examples of this include the *BRCA1* and *BRCA2* genes for hereditary breast ovarian cancer syndrome, and the *HD* gene that leads to Huntington disease. In these circumstances, the testing of minors should, in general, not be pursued. Rather, the decision to undergo genetic testing should rest with the individuals themselves once they reach legal age and ability to consent to such testing. (5) Similarly, there is generally not a compelling reason to do carrier testing of autosomal recessive disorders for minors given that carriers are asymptomatic.

Genetic counselors and medical geneticists are experts in navigating genetic testing options, interpreting results, searching the literature, and communicating the meaning of results to the physician, patient, and/or family member. In addition, they are available as a resource to health-care providers who have questions about how to approach genetic testing. These individuals not only provide assistance and resources but may also help educate health-care providers about the tools available. Furthermore, a new field of genetic counselors that has recently emerged is that of laboratory genetic counselors. These genetic counselors regularly facilitate communication between health-care professionals and the laboratory to ensure that genetic testing is used wisely and correctly (ie, utilization management) and can also assist health-care professionals in understanding complex testing results or in determining appropriate testing options for a patient. (6)

THE DIFFERENCES IN TRAINING AND ROLES BETWEEN GENETIC COUNSELORS AND MEDICAL GENETICISTS

Although geneticists and genetic counselors commonly work as a team in the pediatric setting, they come from different training backgrounds, resulting in different roles, responsibilities, and scopes of practice. Medical geneticists are physicians who have chosen genetics and genomics as a specialty. There are multiple training program routes that can be undertaken: a primary residency program in genetics (categorical residency programs), multiple residency experiences, or combined residency programs. (7) In the categorical residency, an individual must first complete at least a 1-year residency in a program that is accredited by the Accreditation Council for Graduate Medical Education. The first year can be in any specialty, but the more common examples include pediatrics, internal medicine, family medicine, or obstetrics and gynecology. After completion of the 1-year residency, an individual must then complete a 2-year medical genetics residency program with training in disciplines such as reproductive genetics, pediatric and adult genetic disorders, dysmorphology, inborn errors of metabolism, and cancer genetics. Those individuals are then eligible to take board certification examinations for genetics and genomics.

The second option commonly pursued to become a medical geneticist is to first fully complete a residency in a discipline such as a pediatrics or internal medicine then continue on to complete a second 2-year categorical residency in genetics. Individuals opting for this route are able to be board certified in both residency specialty areas.

The third option, combined genetics residencies programs, typically lasts 4 to 5 years. These residencies combine medical genetics with the fields of internal medicine, pediatrics, maternal-fetal medicine, and reproductive endocrinology and infertility. There is some variation in when a physician begins the residency program; internal medicine and pediatric programs start after the completion of medical school, and maternal-fetal medicine and reproductive endocrinology and infertility programs do not start until the completion of an obstetrics and gynecology residency.

Genetic counselors receive a master's degree from an accredited genetic counseling training program. The most common undergraduate degrees for those entering the field are in biology, genetics, and psychology, but there is not a required undergraduate major. Graduate programs in genetic counseling consist of a combination of classroom training and clinical rotations in multiple specialty areas. The classroom training focuses on courses in medical genetics, laboratory genetics, communication, and counseling. Programs often have their own unique, qualities such as curriculum in bioethics, cultural competency, or community engagement. Field practicum experiences vary between programs, but the 3 core specialties consist of prenatal, cancer, and pediatric experiences. As the field of genetic counseling has continued to develop into new specialties, clinical rotations have also emerged in other specialties, such adult genetics, cardiology, neurology, laboratory counseling, and even primary care. In addition to coursework and clinical rotations, genetic counseling graduate students must complete a graduate research project. Most often, these projects are original research projects that can be used to further the field of medical genetics by responding to current questions and needs of the field.

Differences in training and scope of practice allow medical geneticists and genetic counselors in the pediatric setting to have complementary roles. Medical geneticists' roles during an appointment include performing the clinical examination, providing recommendations for testing, ordering and managing medications, and interpreting biochemical results and imaging. Genetic counselors are then able to focus more on family and medical history, education of genetic information, and psychosocial concerns but leave all physical examinations to the medical geneticist.

When to Refer to Medical Genetics

Understanding the differences between geneticists and genetic counselors is necessary in determining the appropriate referral. In the pediatric setting, it is uncommon for a patient to meet solely with a genetic counselor with no involvement by a medical geneticist or other provider. This is because many of these children require an examination as part of the complete evaluation. Most medical genetics practices have genetic counselors working as part of their team. Following are some examples of common reasons for referral to a medical geneticist.

Example 1. *In the clinic today, you saw a 4-year-old boy for a health supervision visit with 7 café-au-lait macules. When you discussed this finding with his mom, she stated that she did not think anything of them because she and her mom have the same "birthmarks." As a pediatrician, you know that this is a good patient to refer due to his physical findings and the possible family history of NF1. Clinical examination and discussion of genetic testing options would be beneficial to the family to determine the risk of additional features related to NF and future management recommendations. A referral to a medical genetics clinic is warranted.*

Example 2. *You are seeing an 8-month-old girl who was born with a congenital heart defect, hypotonia, failure to thrive due to feeding difficulties, and has been delayed in meeting her motor milestones. She recently started rolling 1 direction but is not able to sit without support. Referral to genetics for patients such as this can be helpful in determining whether there is a single* *underlying cause. It is likely that an assortment of tests would be considered or needed to determine whether this child's concerns are related.*

When to Refer to a Genetic Counselor

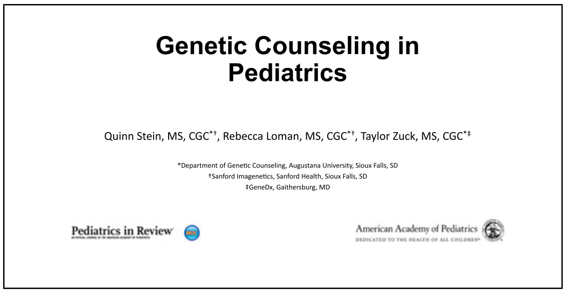
In some situations, a referral directly to a pediatric genetic counselor can be useful. This is especially true if the family previously received a diagnosis but requires more time to discuss the results and condition. Another example includes patients with a family history of a genetic syndrome or a previously affected child who are looking for carrier screening or further discussion of reproductive risks.

When a medical provider is in doubt regarding whether to refer a patient for a medical genetics visit or genetic counseling only visit, it is always appropriate to call and speak to a genetic counselor. By providing the genetic counselor with basic information, he or she is able to help the provider determine the appropriate referral type. For those not familiar with the genetics services in their area, including genetic counselors, a searchable and useful resource is the "Find a Genetic Counselor" tool on the National Society of Genetic Counselors website (searchable by location and specialty type). (8)

Summary

- Genetic counselors are integrated into the pediatric setting by providing direct patient care (ie, meeting face-to-face with families) and by serving as a reliable resource to pediatricians, nurses, administrators, and other members of the health-care team.
- Individuals or families with a genetic condition (or at risk for a genetic condition) commonly seek information about the diagnosis itself, prognosis, management, and implications to the family, thus making education an essential and multifaceted element of genetic counseling.
- Genetic counseling is not the same as genetic testing but rather is a process by which complex genetic information is communicated to patients in an easily understood way.
- At its core, genetic counseling is built on the essential tenet of effective communication—both orally and in writing.
- Informed consent for genetic testing should be voluntary and rooted in patient understanding.
- A genetic counselor presents factual information in a balanced and understandable manner in order for the patient and family to make informed decisions about testing and management, not with the purpose of encouraging or discouraging a particular outcome or decision.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/7/323.supplemental.



Genetic Counseling in Pediatrics

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1. A child with multiple café-au-lait spots is referred to the genetics clinic by his primary care physician. The genetic counselor begins the visit with information gathering. Which of the following is the most appropriate part of the information gathering that is conducted by the genetic counselor on this patient?
   - A. A 3-generation pedigree of targeted family and medical histories.
   - B. Family history of cleft lip with or without cleft palate.
   - C. History of environmental exposures of patient and family members.
   - D. Magnetic resonance imaging of the brain of the patient and his first-degree relatives.
   - E. Punch biopsy of the skin lesions.
2. A 3-year-old boy with infantile spasms, shagreen patches, confetti lesions, and cortical tubers on magnetic resonance imaging is seen in the clinic and diagnosed as having tuberous sclerosis. The managing physician refers him to a genetic counselor for follow-up. Which of the following is the most appropriate area in which the genetic counselor will play a major role in the care of this patient?
   - A. Assist the family with paternity testing.
   - B. Educate the parents by reviewing the patient's clinical diagnosis, the natural history, and the inheritance pattern of tuberous sclerosis.
   - C. Manage the patient's infantile spasms.
   - D. Order genetic testing for tuberous sclerosis for the patient's developmentally normal and clinically asymptomatic 1-year-old female sibling.
   - E. Wood lamp examination of both parents looking for skin findings of tuberous sclerosis in either parent.
3. A newborn female is diagnosed as having phenylketonuria on newborn screening. Confirmatory testing is ordered and the baby is started on a special formula low in phenylalanine. The managing physician discusses the diagnosis with the family and refers the baby to the genetic and metabolic clinic for continued follow-up after discharge from the hospital. At the clinic, the patient and family are seen by a geneticist and a genetic counselor. The genetic counselor is expected to monitor this patient until which of the following times in his life?
   - A. Across the lifespan of the patient.
   - B. One year of age to wean off the special formula.
   - C. Six months of age to educate the family about starting solid foods.
   - D. Until the patient starts school.
   - E. Until the start of the first menstrual period.
4. An 8-year-old boy is seen in the clinic with lens dislocation, aortic root enlargement, and tall stature with long arms. He is diagnosed as having Marfan syndrome. The family is stressed out about the new diagnosis and seems to have many questions. You explain to the parents that the patient will be referred to multiple specialists who will be following him. Which of the following health professionals is more likely to connect the family with support groups related to the new overall diagnosis?
   - A. Cardiologist.
   - B. Child life specialist.
   - C. Genetic counselor.
   - D. Ophthalmologist.
   - E. Psychiatrist.

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5. You are following a 5-year-old girl with short stature and pulmonic stenosis. You suspect Noonan syndrome and refer the family to medical genetics for consultation. The family meets with a clinical geneticist and a genetic counselor. DNA testing for Noonan syndrome is offered to the family. The child's parents are considering having their child tested for mutations in Noonan syndrome–associated genes. Which of the following considerations is the most appropriate to be used by the genetic counselor to help the family decide to proceed with the genetic testing in this patient?
    A. Confirming the diagnosis will not make the clinical situation worse.
    B. Confirming the suspected diagnosis may lead to appropriate changes in medical management.
    C. Testing will confirm paternity.
    D. Testing will improve the patient's insurability.
    E. The genetic test is cheap.

Disorders of the Umbilical Cord

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Education Gap

Clinicians should understand the embryology of the umbilical cord to recognize the signs of congenital and acquired lesions of the umbilical cord to facilitate optimal diagnosis of associated conditions and provide anticipatory guidance regarding cord care.

Objectives

After completing this article, readers should be able to:

1. Understand the embryology and pathophysiology of congenital disorders of the umbilical cord.
2. Characterize common lesions of the umbilical cord and review their presentation, investigations, and management.
3. Counsel parents on the normal course, appearance, and care of the umbilical cord, and provide anticipatory guidance on abnormal appearances of the umbilical cord and its discharge.

Abstract

The umbilical cord, a vital conduit between the placenta and the fetus, loses much of its significance after birth. However, newborns can often present with various abnormalities of the umbilicus, such as benign granulomas or more serious lesions due to persistent remnants, many of which can change the normal course of cord separation and may be associated with significant morbidities if left unrecognized and uncorrected. Although not uncommon, sanguineous drainage from the umbilical stump can be quite alarming to new parents. Parental counseling regarding normal umbilical cord changes, as well as abnormal findings, such as discharge and skin changes, are important for the recognition and timely treatment of potentially significant umbilical cord disorders.

EMBRYONIC DEVELOPMENT OF THE UMBILICAL CORD

Knowledge of umbilical embryology helps one understand how best to recognize and manage congenital disorders of the umbilical cord. At 3 weeks' gestation, the developing embryo is connected to the chorion by a connective stalk, which

AUTHOR DISCLOSURE Drs Muniraman and S. Sardesai and Ms T. Sardesai have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

MD	Meckel diverticulum
OMD	omphalomesenteric duct

contains the developing umbilical vessels and allantois. The primitive gut develops from the yolk sac and is connected, along with vitelline vessels, to the extracoelomic part via the vitelline duct (Fig 1). As the embryo grows, the amniotic cavity expands, drawing the connective stalk and vitelline duct together with proteoglycan-rich Wharton jelly to form the primitive umbilical cord (Fig 1). By the 9th week of gestation, the vitelline duct involutes, whereas the allantois obliterates by the 5th month into the urachus, a fibrous structure that connects the urinary bladder to the umbilicus, to leave behind the umbilical cord composed of 2 umbilical arteries and a single umbilical vein supported by Wharton jelly. (1)(2)(3) Failure of obliteration of allantois and/or the omphalomesenteric duct (OMD) or vessels either completely or partially can lead to congenital disorders of the umbilical cord. The umbilical cord lengthens throughout gestation, from a mean of 12.6 in (32 cm) at 20 weeks' gestation to a mean ± SD of 23.6 ± 4.7 in (60 ± 12 cm) at term, (4) with a mean ± SD circumference of 1.5 ± 0.3 in (3.76 ± 0.7 cm). (5)

After birth, the umbilical cord should be carefully examined for the presence of 3 vessels, vascular abnormalities (including varicosities), hemangioma, and evidence of cord rupture. The incidence of a 2-vessel cord with a single umbilical artery is 0.4% to 0.6% of live births. Although most infants with a single umbilical artery have no coexisting anomalies, approximately 20% to 30% may be associated with congenital abnormalities involving the central nervous, genitourinary, gastrointestinal, or cardiovascular systems. The incidence of renal anomalies associated with a single umbilical artery is 4% to 16%, most of which are minor anomalies and clinically insignificant. Current evidence does not support routine imaging for detecting anomalies in infants with a single umbilical artery; however, these infants should be carefully examined for dysmorphic features and associated anomalies. (6)(7)(8)

SEPARATION OF UMBILICAL CORD

The mechanism of cord separation is not fully understood. After the umbilical cord is cut and clamped, cord separation is thought to be initiated by thrombosis and contraction of the umbilical vessels. This is followed by granulocyte- and phagocyte-mediated necrosis, collagenous degeneration, and infarction of the cord tissue. (9)(10) The stump gradually shrivels, dries, and separates by the end of the first to second postnatal week (mean, 6–13 days). (11)(12)(13)(14) Age at which the cord separates may vary based on factors such as mode of delivery, gestational age, birthweight, and

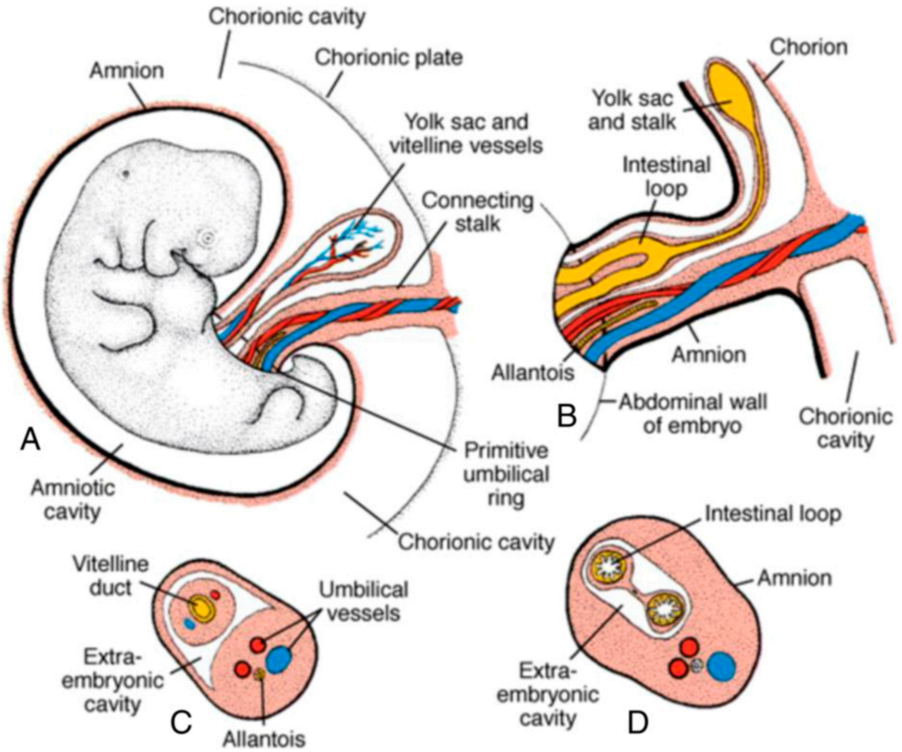


Figure 1. Primitive umbilical cord and contents. A. A 5-week embryo showing structures passing through the primitive umbilical ring. B. The primitive umbilical cord of a 10-week embryo. C. Transverse section through the structures at the level of the umbilical ring. D. Transverse section through the primitive umbilical cord showing intestinal loops protruding in the cord. (Reprinted with permission from Sadler TW. *Langman's Medical Embryology*. 13th ed. Philadelphia, PA: Wolters Kluwer Health; 2015.)

neonatal infections. (11)(12) The timing of umbilical cord separation is often a source of concern to parents. (9)

DELAYED SEPARATION OF UMBILICAL CORD

There is no standard definition of delayed cord separation, probably due to the variations seen in normal cord separation. Separation of the cord beyond 3 weeks of age is generally considered to be significantly delayed. (11)(12) Perinatal factors that are associated with delayed separation of the umbilical cord include prematurity, low birthweight, administration of topical antimicrobial agents, systemic antibiotics for neonatal infections, and delivery by cesarean route. (12)(13)(14) Topical antimicrobials and/or isopropyl alcohol are usually applied after delivery. Studies have shown longer time to separation of the cord with use of antiseptic topical agents such as chlorhexidine, 70% alcohol, and triple dye. (15)(16) In addition to the various umbilical cord care regimens, infections, immune disorders including leukocyte adhesion deficiency, and omphalomesenteric and urachal remnants can delay umbilical cord separation. (17) Although most infants with delayed cord separation do not have infections, (11)(12) infants with delayed cord separation and presentation of omphalitis or skin infections should be investigated for immunologic disorders, including leukocyte adhesion deficiency. (18) Lotus birth or nonseverance of cord is a practice where the umbilical cord is not cut after birth and is allowed to naturally separate, which often takes a few days. However, this practice may be associated with an increased risk of infection, and currently there is no evidence to support this practice. (19)

UMBILICAL GRANULOMA

After the separation of the cord, granulation tissue may persist at the base as a small mass. The tissue, usually light pink in color, is composed of fibroblasts and capillaries and is typically 1 to 10 mm in diameter. Persistent serous or serosanguinous drainage around the umbilicus may be suggestive of an umbilical granuloma. (2)(20)

Conventional treatment of umbilical granulomas includes cauterization with silver nitrate. Generally, only a few applications of silver nitrate are required for successful treatment. (2)(20)(21) Caution should be exercised in applying silver nitrate because of the risk of chemical burns or temporary discoloration of the surrounding skin. (22) Pedunculated umbilical granulomas that do not respond to chemical cauterization may be treated with ligature using absorbable sutures. (23) Persistence of a presumed umbilical granuloma or those that do not resolve with conventional measures may warrant further evaluation to rule out other pathologic abnormalities, including polyps, which require surgical exploration and excision. (2)(20)(21)

OMPHALITIS

Infection of the umbilicus and/or surrounding tissues is referred to as omphalitis. It is usually characterized by an unhealthy, discolored, and craggy-appearing umbilical stump; purulent drainage; periumbilical erythema; and induration. Infants may also have systemic signs of sepsis, including lethargy, irritability, poor feeding, and temperature instability. (24)(25)

The incidence of omphalitis is estimated to be approximately 1 in 1,000 infants in developed countries where aseptic delivery and hygienic dry cord care are practiced. However, the incidence may be as high as 8% in low-income communities or developing countries. (25) The risk factors associated with the development of omphalitis include prolonged rupture of membranes, maternal infection, nonsterile delivery practices, home delivery, and neonatal factors such as umbilical catheterization, low birthweight, improper cord care or cultural practices of cord care (such as application of cow dung, charcoal dust, or products such as cooking oil and baby powder to the cord stump, and lotus births), delayed cord separation, and immunologic conditions, namely, leukocyte adhesion deficiency. (24)(25)(26)(27)(28) *Staphylococcus aureus* is the most reported pathogen causing omphalitis, followed by gram-negative bacteria, including *Escherichia coli* and *Klebsiella*. Other bacteria that have been implicated are group A and B *Streptococcus*, and anaerobic bacteria such as *Clostridium, Bacteroides,* and polymicrobial infections account for a small proportion of omphalitis. (24)(25)(26)(29)

The clinical spectrum of omphalitis ranges from infection limited to the umbilical cord (funisitis presenting with malodorous discharge) and omphalitis with cellulitis of the periumbilical region to a more severe presentation with systemic signs of infection, and in the severest presentation as necrotizing fasciitis with dermal and myonecrosis. Overall mortality is reported to be 7% to 15%, but mortality may be as high as 60% in infants with necrotizing fasciitis. (30)(31) Necrotizing fasciitis starts initially as periumbilical cellulitis and rapidly spreads to the subcutaneous tissues, with the overlying skin appearing edematous with purplish-blue discoloration. Necrotizing fasciitis may also present with bullae, crepitus and peau d'orange appearance. (31)

Complications of omphalitis include umbilical venous phlebitis, portal vein thrombosis, intra-abdominal and retroperitoneal abscess, peritonitis, peritoneal adhesions, and bowel ischemia. (30) Management of omphalitis should include umbilical stump and skin cultures, as well as a full sepsis evaluation, including lumbar puncture in infants with systemic signs. Parenteral broad-spectrum antibiotics such as a combination of clindamycin and cefotaxime or gentamicin should be initiated empirically, and the area of cellulitis marked and closely followed. The antibiotics are generally continued for 10 days, and a longer course may be required for severe infections. In communities with a high prevalence of methicillin-resistant *S aureus*, vancomycin should be used. Metronidazole or piperacillin/tazobactam should be considered to provide coverage against anaerobic bacteria if there is a concern of systemic infection or necrotizing fasciitis. (32) Necrotizing fasciitis should be recognized early and treated aggressively by debridement, broad-spectrum antibiotics, and supportive care. (21)

OMPHALOMESENTERIC (VITELLINE) REMNANT

Omphalomesenteric duct anomalies result from partial or complete failure of obliteration of the OMD that connects the yolk sac to the gut in the embryo. The exact etiology of incomplete obliteration remains unknown. Persistence of OMD occurs in 2% to 3% of children (33) and, depending on the degree and location of involution, has a variety of anatomical patterns that include vitelline cyst (patent central portion, Fig 2 A and D), umbilical sinus (patent at umbilical end, Fig 2B), umbilical polyp (mucosal remnant at umbilicus, Fig 2C), Meckel diverticulum (MD) (partially patent at intestinal end, Fig 2E), and completely patent duct (omphalomesenteric fistula, Fig 2F). Although OMD remnants are usually asymptomatic, 40% of these lesions may present with symptoms, including gastrointestinal bleeding, intestinal obstruction, and umbilical abnormalities, depending on the specific type of defect. (34) The simultaneous presence of more than 1 anomaly of OMD in the same patient has also been reported. (35)

Meckel diverticulum is the most common anomaly resulting from incomplete obliteration of the OMD. An estimated overall prevalence of MD in the general population is 0.6% to 4%. (36) The rule of 2s is a useful aid in MD's description because MD occurs in 2% of the population, appears within 2 feet of the ileocecal valve, is 2 in long, approximately 2% to 4% of patients develop complications over the course of their lives, and typically presents before age 2 years. (20) Two-thirds of patients with MD have 2 types

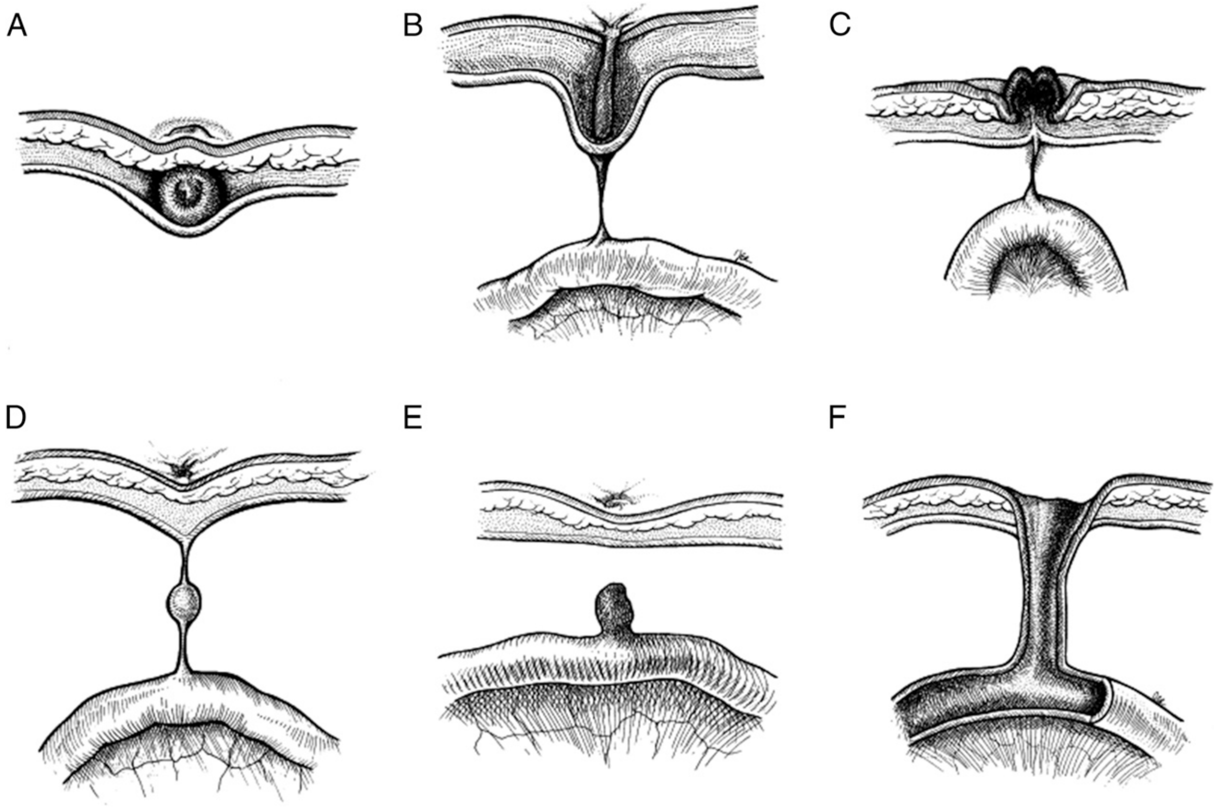


Figure 2. Omphalomesenteric duct remnants. A. An umbilical cyst containing intestinal tissue. B. Umbilical sinus with a band. C. Umbilical polyp covered with intestinal mucosa. D. Fibrous band containing a cyst. E. Meckel diverticulum. F. Patent omphalomesenteric duct. (Reprinted with permission from Ciley R. Disorders of the umbilicus. In: *Pediatric Surgery.* 7th ed. Philadelphia, PA: Elsevier; 2012:961–962.)

of heterotopic mucosa (gastric and pancreatic), although colonic heterotopic mucosa has also been reported. Most MD is asymptomatic. Clinical presentations include lower gastrointestinal bleeding due to ulceration of the heterotopic gastric mucosa and intestinal obstruction due to intussusception or volvulus. (2)(16) Technetium 99 scan, or Meckel scan, is the most commonly used modality for detecting heterotopic gastric mucosa associated with MD. Radiologists may use histamine-2 receptor blockers as an adjunct to Meckel scan to improve the diagnostic yield, especially in cases of profuse gastrointestinal bleeding, by enhancing visualization of the contrast. (20)(37) Additional diagnostic evaluations, such as ultrasonography, computed tomographic scan, upper gastrointestinal barium studies, or selective angiography, may be considered. However, some infants with negative imaging and a high degree of suspicion may require exploratory laparotomy. (20)(38)

Patent OMD (umbilical enteric fistula), a patent conduit connecting the umbilicus to the ileum, is one of the least common variants of OMD anomalies and usually presents with minimal but persistent discharge of intestinal contents or stool at the umbilicus (Fig 3). Diagnosis is usually made during infancy as feces or bilious drainage is noted at the umbilicus. (2)(20) Severe, erosive dermatitis may occur in the skin adjacent to the umbilicus due to the irritating effects of fecal drainage. Accidental intestinal perforation and pneumoperitoneum have been reported during umbilical vessel catheterization in the neonatal period. (39) The umbilical cord should be carefully examined at birth and during catheterization by health-care professionals performing these tasks to prevent such complications. The recommended technique for placement of umbilical catheters can be viewed from the referenced video. (40)

Umbilical cysts may present as a firm, erythematous, cystic swelling at the umbilicus but are typically asymptomatic. In some cases, they may present with bowel obstruction or infection. (2) An OMD sinus should be suspected when mucus discharge is noted in the presence of an umbilical polyp or granuloma. (2)(20) Patent OMD may be identified early in the neonatal period due to persistent feculent discharge. However, cysts and sinus tract may require additional evaluation, including ultrasonography and fistulography. Management involves surgical exploration to exclude associated OMD or urachal remnants and excision of the duct. (2)(20)(21)

UMBILICAL POLYP

An umbilical polyp is a remnant of OMD or urachal embryologic remnant (Fig 4). An umbilical polyp may coexist with OMD or urachal sinus, cyst, fistula, or a band and may be associated with urine or fecal discharge. (33)(38)

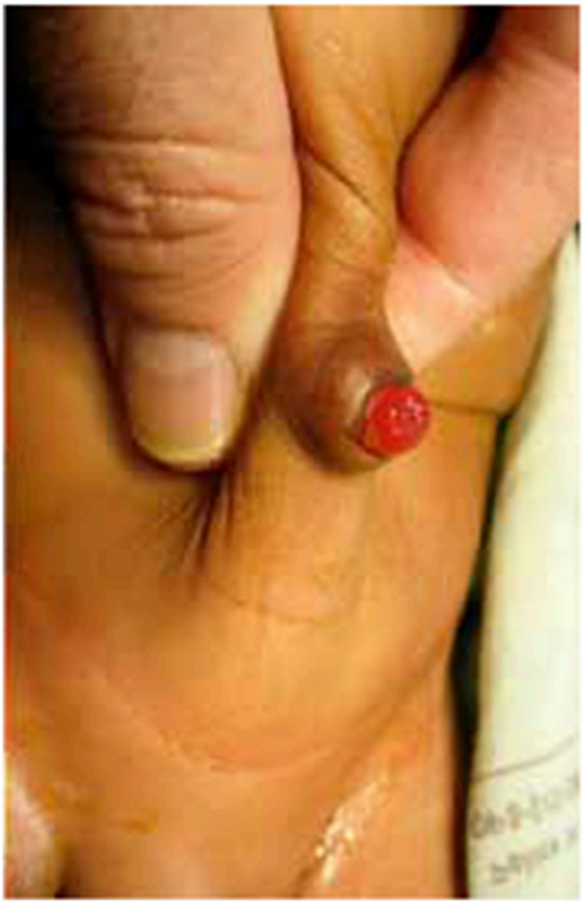


Figure 3. Patent omphalomesenteric duct. (Reprinted with permission from Rakotomalala JH, Poenaru D, Mayforth RD. Disorders of the umbilicus. In: *Paediatric Surgery: A Comprehensive Text for Africa.* Seattle, WA: Global HELP; 2010:353; www.global-help.org.)

Umbilical polyps present as a bright red, firm, painless mass with mucoid/bloody discharge. They may be mistaken clinically for umbilical granulomas or pyogenic granulomas, which may have a pink or velvety appearance. Unlike umbilical granulomas, umbilical polyps do not respond to chemical cauterization. Histopathologic evaluation is warranted if there is any doubt whether an umbilical mass in a neonate is a polyp or granuloma. If a polyp is diagnosed, further evaluation for associated embryologic anomalies (eg, MD) should be performed. Umbilical polyps are associated with an underlying OMD anomaly in 30% to 60% of patients. (20) In such conditions, ultrasonography or fistulography may be beneficial. Early diagnosis and treatment of an umbilical polyp may decrease the risk of associated complications.

URACHAL ANOMALIES

The urachus normally obliterates by 5 months of gestation to become the median umbilical ligament. Failure of urachal

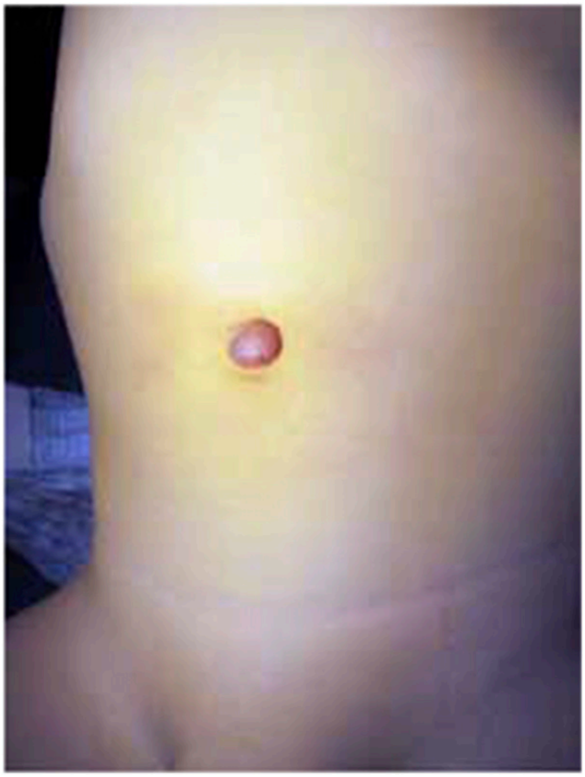


Figure 4. Umbilical polyp. (Reprinted with permission from Rakotomalala JH, Poenaru D, Mayforth RD. Disorders of the umbilicus. In: *Paediatric Surgery: A Comprehensive Text for Africa.* Seattle, WA: Global HELP; 2010:354; www.global-help.org.)

obliteration leads to urachal anomalies. Depending on the degree of involution, a variety of anatomical patterns may occur, including a complete patent urachus, partially patent urachus at the umbilical end (urachal sinus), patent central portion (urachal cyst), urachal remnant at bladder (bladder diverticulum), or mucosal remnant at the umbilicus (umbilical polyp). (2)(20)

The true incidence of urachal anomalies is not known, as most anomalies are reported as incidental findings in patients undergoing imaging for unrelated indications. A recent retrospective study estimated the prevalence of urachal anomalies to be approximately 1% in the general pediatric population, with ultrasonography being the most common imaging modality in diagnosing urachal anomalies. (41)(42) In those who present with symptoms, clear discharge from the umbilicus is the most common presentation, followed by a mass or cyst. Rare presentations include pain and retraction of the umbilicus during voiding. (2) A giant umbilical cord as an initial presentation of a patent urachus has been described. (43)(44) Urinary ascites due to spontaneous rupture or perforation of the urachus during umbilical catheterization has also been described, highlighting the importance of closely examining the umbilical cord before performing the procedure. (45) Simultaneous presence of stool and urine should increase suspicion for the presence of a patent OMD with a coexisting patent urachus.

Complications of urachal anomalies include infection calculus formation, urinary ascites, peritonitis, and an increased risk of malignancy such as adenocarcinoma of the bladder. (2)(20)(41)

Ultrasonography is the preferred modality of imaging for urachal anomalies and can help make the diagnosis in most patients. Magnetic resonance imaging or computed tomographic scan may be considered when ultrasonography is nondiagnostic. A sinogram with injection of radiocontrast material into the urachal opening may be used to identify the presence of a patent urachus or sinus tract. Renal ultrasonography and voiding cystourethrography should be considered to evaluate for associated renal and lower urinary tract obstructions such as a posterior urethral valve. (2)(20)(46)

An infected urachal cyst is initially treated with antibiotics, followed by complete excision. Surgical excision is recommended to prevent recurrent infections in cases of persistent symptoms. To prevent the development of urachal adenocarcinoma, complete surgical excision of the entire lesion, including the cuff of the bladder, has been the recommended treatment for a patent urachus. (2)(20) However, more recent literature has demonstrated a much higher incidence of asymptomatic anomalies and has questioned the benefit of surgery in asymptomatic children. Based on some research evidence as well as consensus, it is generally agreed that symptomatic urachal diverticula must be surgically treated, whereas asymptomatic and uncomplicated urachal diverticula require close monitoring. (41)

UMBILICAL HERNIA

During fetal life, a fascial opening with a fibrous ring in the abdominal wall functions as a channel that allows blood flow between the placenta and fetus. As the gestation progresses, the umbilical ring contracts and eventually closes after birth, with separation of the cord and fusion of the rectus abdominis muscle. Posteriorly, the umbilical opening is covered by Richet fascia and peritoneum. The umbilical ring is also reinforced superiorly by a round ligament and inferiorly by median and medial ligaments. Complete or partial failure of attachment by Richet fascia or the ligaments may weaken the umbilical ring and result in the development of an umbilical hernia. Umbilical hernias are protrusions of the peritoneum covered by skin and may contain peritoneal fluid, fat, intestine, or omentum. (2)(20)

A higher incidence of umbilical hernias is seen in African American infants and in infants with Beckwith-Wiedemann syndrome, trisomy 21, congenital hypothyroidism, and mucopolysaccharidoses. Umbilical hernias are much more common in preterm infants, with some studies reporting as many as three-fourths of infants with very low birthweight having umbilical hernias. (2)(16)(47)

Umbilical hernias can be easily diagnosed during the newborn abdominal examination, particularly during periods of crying when there is increased intra-abdominal pressure. Umbilical hernias are easily reduced, even if they are quite large, and the borders of the fascial defects can be palpated through the skin.

Most hernias close spontaneously during the first 3 years of life, and most will close by 6 years of age, although closure at up to 14 years of age has been reported in African American children. A factor that supports spontaneous closure is a smaller diameter size of the fascial defect rather than the size of the hernia. Most hernias with defects less than 1 cm close spontaneously, whereas hernias with defects larger than 1.5 cm are less likely to close spontaneously. (47)(48)(49)(50) Complications, including incarceration, strangulation, and rupture of umbilical hernias, may occur rarely.

Due to the high rate of spontaneous closure, conservative management with reassurance and observation are sufficient, and repair is deferred until age 5 years at most institutions. Early closure is indicated if the defect is larger than 1.5 cm; in children with large, proboscoid (trunk-like) hernias without any decrease in the size of the umbilical ring defect over time; or in the rare instance of complications associated with umbilical hernias. (2)(20)(21)

HERNIA OF THE UMBILICAL CORD

A small omphalocele may present as herniation of abdominal viscera through the umbilical ring at the base of the umbilical cord. (2) If missed, this condition can lead to intestinal damage by a low-placed umbilical cord clamp. Approximately 70% of infants with omphalocele have associated anomalies, including cardiac, genitourinary system, or spinal abnormalities. Thirty percent of affected infants have associated chromosomal abnormalities, with 10% of infants having Beckwith-Wiedemann syndrome. (51) Small omphaloceles require prompt surgical closure and evaluation for associated anomalies. (21)

BLEEDING FROM UMBILICAL CORD

Persistent and prolonged bleeding from the umbilical cord is abnormal and should raise suspicion of coagulation abnormalities such as factor II, factor X, and factor XIII deficiency. Factor XIII almost exclusively presents with umbilical cord bleeding in the neonatal period and may present along with intracranial hemorrhage. (52)(53)

CORD CARE

Colonization of the umbilical cord with pathogenic bacteria has been implicated in omphalitis, sepsis, and neonatal morbidity. The umbilical stump can provide an optimal media for growth of pathogens, and with direct communication with neonatal blood vessels, there is a high risk of invasive bacteremia. With practice of good hygiene and aseptic delivery, risk of colonization with pathogenic bacteria has been reduced considerably in high-resource countries. (25) In low-resource communities and in developing countries, use of antiseptic solutions such as chlorhexidine has been shown to reduce omphalitis/infection by half and neonatal mortality by 12%. However, the routine use of chlorhexidine in infants born in hospitals and birthing centers in resource-rich countries has not been shown to be beneficial. (54)

The World Health Organization and the American Academy of Pediatrics recommend dry cord care for infants born in hospitals in high-resource countries.(25)(55) “Dry cord care involves keeping the cord clean and dry by exposure to room air or with light clothing with no application of antiseptic or antimicrobial agents. Chlorhexidine may be considered for unplanned home births or low resource communities. Gentle washing with soap and sterile water has been recommended for a soiled umbilical cord.” (25)

ACKNOWLEDGMENT

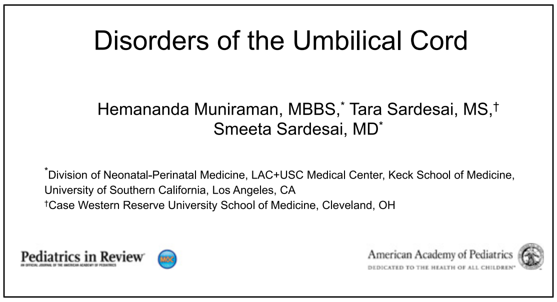
We thank the editor and the 2 anonymous reviewers for their insightful suggestions and comments.

Summary

- Based on strong research evidence as well as consensus, dry cord care should be considered for infants born in hospitals and birthing centers and after planned home births because use of antimicrobial agents does not provide additional benefits. Whereas in resource-limited communities and unplanned home births, prophylactic topical antimicrobial agents may be beneficial in reducing the risk of omphalitis. (25)(54)(55)

- Based on moderate research evidence as well as consensus, infants with suspected or confirmed umbilical polyps, omphalomesenteric ducts, and urachal remnants should be referred promptly to pediatric surgeons for surgical evaluation. (20)(21)
- Based on moderate evidence as well as consensus, an umbilical granuloma may be treated with topical silver nitrate. Surgical referral may be warranted for large pedunculated granulomas or for those who do not respond to topical treatment. (20)(21)
- Based on strong research evidence as well as consensus, and due to high risk of mortality and morbidity associated with omphalitis and its complications, omphalitis should be treated aggressively with parenteral antibiotics. (20)(21)(25)
- Parental education and anticipatory guidance to parents regarding cord care, the normal course of cord separation, abnormal discharge, and signs and symptoms of omphalitis may result in early recognition and prompt medical attention, which may help reduce morbidities. (25)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/7/332.supplemental.


Disorders of the Umbilical Cord

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1. When admitting a term newborn to the well-baby nursery, you notice that the baby has a 2-vessel cord with a single umbilical artery. You prepare to discuss the finding with the parents. Which best describes the most appropriate next step in the management of this patient?
   - A. Abdominal ultrasonography.
   - B. Full physical examination.
   - C. Head ultrasonography.
   - D. Reassurance.
   - E. Renal ultrasonography.
2. A 1-month-old, well-appearing term baby boy is seen in the clinic for a health maintenance visit. During the physical examination, the parents point out that the umbilical cord has not yet separated. In obtaining further history, the physician confirms that they have not applied any topical agents to the cord since birth and have been practicing dry cord care. On physical examination, there is mild periumbilical erythema and purulent drainage. The remainder of the examination findings are normal. Investigations for which of the following disorders should be considered for this child?
   - A. Collagen type IV disorders (COL4A).
   - B. Factor XIII deficiency.
   - C. Leukocyte adhesion deficiency.
   - D. Omphalomesenteric duct anomalies.
   - E. Umbilical hernia.
3. A 1-week-old newborn is brought to urgent care with a concern about drainage from the umbilicus. On further history, the parents report that they have been carefully applying baby oil to the cord stump daily. On physical examination, the baby has normal vital signs and is irritable. Purulent drainage is noted from the umbilical stump, and there is periumbilical skin erythema and tenderness. Which of the following is the most appropriate next step in the management of this baby?
   - A. Skin surface culture, and starting oral antibiotics.
   - B. Skin surface culture warm compresses, and application of topical antibiotics.
   - C. Complete blood cell count; blood, urine, and cerebrospinal fluid cultures; and initiation of parenteral antibiotics.
   - D. Marking of area of erythema with instructions to return in 3 to 5 days for follow-up.
   - E. Chlorhexidine washes to the area, reassurance, and education regarding dry cord care.
4. A 6-month-old girl is brought to urgent care with lower gastrointestinal bleeding. She had been seen at the same office with the same problem a month earlier, at which time results of abdominal ultrasonography were negative. She is afebrile, with stable vital signs. On physical examination, she has no abdominal tenderness or distention, and no masses are palpated. The potential diagnosis of Meckel diverticulum is suspected. Which of the following approaches is most commonly used for detecting heterotopic gastric mucosa associated with Meckel diverticulum?
   - A. Colonoscopy.
   - B. Exploratory laparotomy.
   - C. Magnetic resonance imaging.
   - D. Technetium 99 scan.
   - E. Ultrasonography-guided biopsy.

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5. You meet a first-time mother in the postpartum ward after an uncomplicated delivery of a term baby boy. His examination findings are normal. The mother asks you what she should do to take care of the umbilical stump after going home because relatives have advised various regimens to her. Which of the following is the recommended measure by the World Health Organization and the American Academy of Pediatrics for cord care for infants born in hospitals in high-resource countries?
    - A. Application of baby powder to facilitate cord drying.
    - B. Covering the cord with gauze to avoid infection.
    - C. Daily application of topical antimicrobial agents.
    - D. Gentle washing with soap and sterile water if the cord becomes soiled.
    - E. Vigorous cleansing with 70% alcohol with each diaper change.

Vomiting in Children

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Education Gaps

1. There are at least 4 known physiologic pathways that can trigger vomiting, 3 of which are extraintestinal.
2. Understanding which pathway is causing a patient's vomiting will help determine best treatment options, including which antiemetic is most likely to be helpful to mitigate symptoms.
3. Bilious emesis in a newborn should indicate bowel obstruction.
4. Cyclic episodes of vomiting may be indicative of a migraine variant.

Objectives After completing this article, readers should be able to:

1. Understand the main pathways that trigger vomiting via the emetic reflex.
2. Differentiate among acute, chronic, and cyclic causes of vomiting.
3. Create a broad differential diagnosis for vomiting based on a patient's history, physical examination findings, and age.
4. Recognize red flag signs and symptoms of vomiting that require emergent evaluation.
5. Recognize when to begin an antiemetic medication.
6. Select antiemetic medications according to the presumed underlying mechanism of vomiting.

Vomiting is a common symptom of numerous underlying conditions for which children frequently present for healthcare. Although vomiting can originate from the gastrointestinal (GI) tract itself, it can also signal more generalized, systemic disorders. Vomiting in children is often benign and can be managed with supportive measures only. Still, clinicians must be able to recognize life-threatening causes of vomiting and to avoid serious associated complications, including electrolyte abnormalities, dehydration, or even bowel necrosis.

DEFINITIONS

Vomiting is defined as the *forceful* expulsion of gastric contents through the mouth and/or nose. Vomiting differs from gastroesophageal reflux (GER) and regurgitation in

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ABBREVIATIONS

5-HT	5-hydroxytryptamine
CHS	cannabinoid hyperemesis syndrome
CTZ	chemoreceptor trigger zone
CVS	cyclic vomiting syndrome
EGD	esophagogastroduodenoscopy
FPIES	food protein–induced enterocolitis syndrome
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
IEM	inborn error of metabolism
PS	pyloric stenosis
SMA	superior mesenteric artery

that the latter 2 conditions are characterized by *effortless* retrograde flow of duodenal or gastric fluids into the esophagus and oral cavity. Vomiting is also different from rumination syndrome, in which patients self-promote to electively regurgitate, and often chew and swallow their regurgitated food again.

PATHOPHYSIOLOGY

Vomiting is the end point of the emetic reflex, a neuropathic process by which the body protects itself against toxins, intestinal distention, and a myriad of other triggers. The emetic reflex is mediated by the central processing unit in the brain, which consists of the chemoreceptor trigger zone (CTZ), the dorsal motor vagal nucleus, and the nucleus of the tractus solitarius. The central processing unit is often also referred to as the "vomiting center" of the brain. However, this may be a misnomer as the central processing unit is not an anatomically differentiated region, and instead is best conceptualized as physiologically connected neurologic components that work together to stimulate the emetic reflex (Fig 1).

Once a stimulus to vomit has been received by the central processing unit, retrograde contractions of the intestine are initiated and coordinated by the vagus nerve. Before retching, a retrograde giant intestinal contraction forces duodenal fluid into the stomach.

Retching begins when the upper esophageal sphincter and glottis close, and the diaphragm, external intercostal muscles, and abdominal muscles contract strongly together. Subsequently, elevated positive pressure in the abdominal cavity is generated and the esophagus contracts and then dilates. This allows a relaxed stomach to be drawn up into the thoracic cavity, effectively removing the antireflux ability of the lower esophageal sphincter. With each cycle of retching, intra-abdominal pressure is increased, and intestinal contents are pushed closer to the oral cavity, until they are eventually expelled.

The Pathways that Cause Vomiting

There are 4 main stimulating pathways that can induce the emetic reflex: mechanical, blood-borne toxins, motion, and

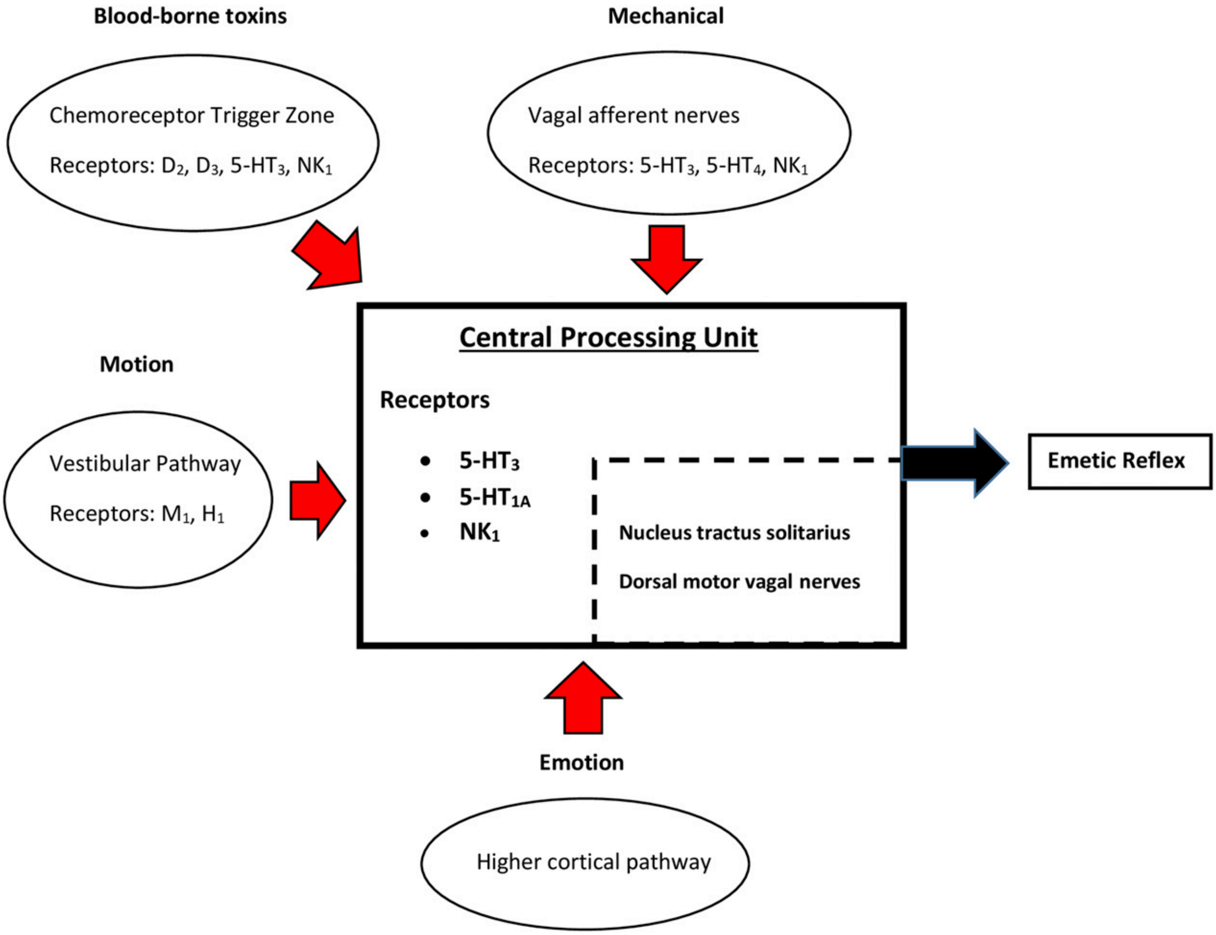

Figure 1. The various physiologic pathways and cellular receptors that can trigger vomiting. 5-HT=5-hydroxytryptamine, NK1=neurokinin 1.

emotional response. (1) Each pathway includes 1 or multiple receptors activated by various specific neurotransmitters and can occur either in isolation or in combination. For most children with vomiting, regardless of pathway induced, no treatment is necessary. However, a variety of neurotransmitter receptors have become the targets of antiemetic medications. Understanding which of the 4 pathways may be involved is the key to selecting an antiemetic medication that will most likely alleviate vomiting. Even if symptoms improve, it is still critical to look for the underlying cause.

Mechanical. The mechanical pathway is activated when either mechanoreceptors or chemoreceptors in the gut wall are stimulated. Mechanoreceptors in the intestine are responsible for monitoring the amount that the bowel distends. If a child eats too much or if the bowel becomes obstructed, mechanoreceptors will sense stretched mucosa and stimulate vagal afferents through the activation of 5-hydroxytryptamine (5-HT_3, 5-HT_4) and neurokinin 1 receptors. In turn, the central processing unit stimulates the efferent (motor) limb of the emetic reflex. The mechanical pathway is also activated when chemoreceptors in the wall of the intestine sense the presence of an irritant. Irritants may include cellular byproducts or toxins, such as those involved in food poisoning.

Blood-borne Toxins. Blood-borne toxins target receptors in the CTZ of the area postrema. These chemoreceptors can also be triggered by substance P, a neuropeptide produced by the body in response to neurotoxic agents and other stressors. Binding of substance P to neurokinin 1 receptors can induce the emetic reflex.

The CTZ is found in the floor of the fourth ventricle, which itself lies in the medulla oblongata. It is not protected by the blood-brain barrier and can easily recognize toxins. The CTZ includes various neuroreceptors, including dopamine receptors D_2 and D_3, 5-HT_3, and neurokinin 1. An example of a blood-borne toxin is the chemotherapeutic drug cisplatin, which is known to significantly increase serotonin levels that activate 5-HT_3 receptors peripherally and centrally in the CTZ. (1)

Motion. Aberrant motion of the human body can stimulate vomiting via the vestibular system, which is critical for maintaining our perception of our body position with relationship to the environment. If this perception becomes altered, such as when riding in a car, muscarinic and histamine receptors can be activated, triggering the emetic reflex.

Emotional Response. Some patients will vomit in response to strong emotions such as anxiety, fear, or even strong smells. Emesis in emotional responses is thought to be mediated by release of corticotrophin-releasing factor.

Causes of vomiting may stimulate more than 1 pathway, but there is usually 1 pathway that predominates. Table 1 lists the differential diagnosis of vomiting broken down by primary pathway.

DIFFERENTIATING BETWEEN CAUSES OF VOMITING BY AGE AND DEFINING CHARACTERISTICS

The list of causes of vomiting is extensive and includes common, benign disorders, such as viral gastroenteritis, as well as rare, life-threatening conditions, such as intussusception. In some circumstances, the actual cause of vomiting might not represent an emergency, but the consequences of excessive fluid loss can include severe dehydration or electrolyte abnormalities, including hypochloremia and/or hypokalemia. Identifying the cause of vomiting, even when benign, may, therefore, be critical, because ideally this will allow therapeutic efforts to be targeted to prevent ongoing symptoms, as well as complications.

One approach to organizing the differential diagnosis of vomiting in pediatrics can be by age and symptom pattern. The latter can generally be categorized according to whether it represents acute, chronic or cyclic vomiting (Table 2).

Acute Vomiting

Acute vomiting presents rapidly over 24 to 48 hours and can be associated with severe symptoms and dehydration. Causes of acute vomiting include viral gastroenteritis, food poisoning, or bowel obstruction. Acute vomiting can be self-limited or can recur episodically. Examples of conditions with a symptom pattern of acute, episodic vomiting include intestinal malrotation with intermittent volvulus, inborn errors of metabolism (IEMs), and food protein–induced enterocolitis syndrome (FPIES). Cannabinoid hyperemesis syndrome (CHS) is another newly recognized diagnosis associated with severe, episodic vomiting that may be more common than previously appreciated in adolescent populations.

Chronic Vomiting

Chronic vomiting is seen in children who have had symptoms for several days to weeks. Chronic vomiting tends to be of low volume and infrequent, and it is rarely associated with dehydration. Causes of chronic vomiting include peptic ulcer disease, gall bladder disease, eosinophilic esophagitis, gastritis, and adverse reactions to ingested foods.

TABLE 1. **Causes of Vomiting by Pathway**

MECHANICAL	BLOOD-BORNE TOXINS
Annular pancreas	Acute intermittent porphyria
Appendicitis	Adrenal insufficiency
Bezoar	Alcohol
Celiac disease	Carcinoid syndrome
Choledocholithiasis	Chemotherapeutic agent
Choledochal cyst	Diabetic ketoacidosis
Cholelithiasis	Fatty acid oxidation defect
Constipation	Food poisoning
Duodenal hematoma	FPIES
Eosinophilic esophagitis	Galactosemia
Esophageal achalasia	Hereditary fructose intolerance
Foreign body	Hypercalcemia
Gastritis	Hyperthyroidism
Gastroparesis	Liver failure
GERD	Marijuana/CHS
Hirschsprung disease	MCAD deficiency
Hydronephrosis	Medications
Ileus	Cisplatin
Infections	Digoxin
Acute otitis media	Opioids
Gastroenteritis	Theophylline
Hepatitis/hepatic abscess	OTC deficiency
Meningitis	Pharyngitis
Pharyngitis	Phenylketonuria
Pyelonephritis	Pregnancy
Pneumonia	Pyruvate carboxylate deficiency
Sinusitis	Renal tubular acidoses
Intestinal atresia	Tyrosinemia type 1
Intestinal stricture/obstruction	Urea cycle defects
Intracranial tumor	Uremia
Intussusception	
Malrotation with volvulus	
Nephrolithiasis	
Pancreatitis	
Peritonitis	

Continued

TABLE 1. (Continued)

MECHANICAL	
Pseudo-obstruction	
Pseudotumor	
Pyloric stenosis	
SMA syndrome	
UPJ obstruction	
MOTION/VESTIBULAR RESPONSE	**EMOTIONAL RESPONSE**
Abdominal migraine	Anger
Cyclic vomiting syndrome	Anxiety
Meniere disease	Eating disorder
Migraine headache	Fear
Motion sickness	Psychogenic vomiting
	Strong smell/taste

CHS=cannabinoid hyperemesis syndrome, FPIES=food protein–induced enterocolitis syndrome, GERD=gastroesophageal reflux disease, MCAD=medium-chain acyl-CoA dehydrogenase, OTC=ornithine transcarbamylase, SMA=superior mesenteric artery, UPJ=ureteropelvic junction.

Cyclic Vomiting

Cyclic vomiting is characterized by both symptomatic periods with a sudden onset, as well as by asymptomatic periods between episodes. It is important to differentiate between cyclic vomiting and episodic vomiting. Although intervals between symptoms may vary, cyclic vomiting is characterized by its stereotypical episodes and repetitive nature. The most common etiology of cyclic vomiting is cyclic vomiting syndrome (CVS), a migraine variant that typically involves severe episodes of recurrent retching and emesis, leading children to become lethargic and struggle to tolerate oral fluids.

OBTAINING A MEDICAL HISTORY IN PATIENTS PRESENTING WITH VOMITING

When taking a medical history about pediatric vomiting, one should begin by asking about characteristics of the emesis. When did it begin? How often does it occur? Has it happened before? Is it forceful or effortless? Does it contain bile or blood?

It can be helpful to have the patient or patient's family identify the color of vomitus by using a color card. Bilious emesis in an infant always warrants emergent evaluation to exclude a bowel obstruction.

It is important to realize that color alone is not a specific sign and is not pathognomonic of any particular diagnosis. Although emesis that is characterized from first presentation by being bilious or forceful may be suggestive of bowel obstruction, repeated bouts of vomiting, such as that seen in CVS, can result in the bile-colored reflux of duodenal fluid contents into the stomach. Gastric fluid is often yellow-tinged.

If there are reports of or witnessed blood in the emesis, it can be useful to determine whether the blood is bright red or coffee-ground. Bright red blood that is noticeable immediately with the first bout of emesis may be more consistent with active bleeding that is seen due to ruptured esophageal varices or an ingestion. In contrast, coffee-ground emesis is generally suggestive of a slow bleed or oozing, such as that seen with gastritis or peptic ulcer disease. Blood itself acts as an emetic, likely by triggering chemoreceptors. The presence of blood in vomitus in relationship to other symptoms is also important. Blood that develops after initial episodes of retching or emesis may be suggestive of a Mallory-Weiss tear.

The temporal relationship between food ingestion and vomiting may also provide clues to a diagnosis. Vomiting that begins immediately after eating may be suggestive of an esophageal etiology. This may be particularly the case if the vomitus contains undigested food, which can be caused by eosinophilic esophagitis or achalasia. In contrast, vomitus that includes food and that begins several minutes or hours after eating may be consistent with a gastric source or even gastroparesis. Vomiting from gastroparesis rarely presents without accompanying complaints

TABLE 2. **Causes of Vomiting by Age and Temporal Pattern**

	AGE				
PATTERN	**0-1 MO**	**1–12 MO**	**1–4 Y**	**5–11 Y**	**12–18 Y**
Acute	- FPIES - Hirschsprung disease - Intestinal atresia - Meningitis - Pyloric stenosis - Sepsis	- Foreign body - FPIES - Gastroenteritis - Intussusception - UTI	- Foreign body - Gastroenteritis - Pharyngitis - Toxic ingestion - UTI - Constipation	- Appendicitis - Diabetic ketoacidosis - Pancreatitis	- Choledocholithiasis - Diabetic ketoacidosis - Drug overdose
Chronic	- Adrenal insufficiency - GERD - Hirschsprung disease - Intestinal atresia	- GERD	- Celiac disease - Eosinophilic esophagitis	- Celiac disease - Eosinophilic esophagitis - Gastritis +/- *Helicobacter pylori* - Gastroparesis - PUD	- Bezoar - CHS/marijuana use - Pregnancy
Cyclic	- Adrenal insufficiency - IEMs - Malrotation with volvulus	- Adrenal insufficiency - IEMs - Intussusception - Malrotation with volvulus	- Adrenal insufficiency - Constipation	- Abdominal migraine - Cyclic vomiting syndrome - UPJ obstruction	- Abdominal migraine - CHS/marijuana use - Cyclic vomiting syndrome - Eating disorder - SMA syndrome - UPJ obstruction

CHS=cannabinoid hyperemesis syndrome, FPIES=food protein–induced enterocolitis syndrome, GERD=gastroesophageal reflux disease, IEM=inborn error of metabolism, PUD=peptic ulcer disease, SMA=superior mesenteric artery, UPJ=ureteropelvic junction, UTI=urinary tract infection.

of chronic nausea and early satiety. Vomiting after repeated bouts of fasting or with a large protein meal may be suggestive of IEMs. Vomiting after ingestion of fatty foods may suggest a biliary origin, including gallstones.

If abdominal pain is present, questions that can help to clarify its localization become critical. Lower abdominal pain may be consistent with constipation, inflammatory bowel disease, or kidney disease. Epigastric abdominal pain may suggest gastritis, peptic ulcer disease, or pancreatitis. Right upper quadrant pain is more consistent with hepatobiliary disease, including gallstones or hepatitis. Understanding the relationships between food consumption and the onset of pain may also provide clues. Pain associated with vomiting that resolves after eating may be consistent with a gastric ulcer. Pain that worsens with food may be suggestive of eosinophilic GI disease or a functional GI condition, such as functional dyspepsia. Patients with lactose intolerance generally present with diffuse abdominal pain, bloating, and nausea within 1 to 2 hours after exposure to lactose. Shortly thereafter, they usually describe urgency to "run to the bathroom" and may pass loose stools or diarrhea. They usually do not present with vomiting.

Increased intracranial pressure may be accompanied by headaches or focal neurologic deficits, which may help to differentiate intracranial mass effect due to ominous diagnoses from more benign conditions, such as abdominal migraine. Patients with increased intracranial pressure that occurs due to hydrocephalus, intracranial mass, or pseudotumor cerebri may exhibit a change in mental status, cranial nerve palsies, and visual disturbances. Inborn errors of metabolism will also often present with a change in mental status and should be considered in patients with developmental or growth delay. Intussusception can also present with lethargy and a history of sporadic vomiting.

A review of medications in the home, recent travel, and family history of migraines may be helpful in establishing a diagnosis. Vomiting that wakes a child from sleep is always concerning and should be investigated for underlying etiologies that may be life-threatening. On the other hand, a classic sign of abdominal migraine may be early morning vomiting. Chronic sinusitis can also result in morning vomiting. These patients often awake from sleep and then, within a few minutes of wakening, will vomit mucus, often in association with coughing.

Posttussive emesis is common in children and occurs due to increased abdominal pressure. It is important to consider GI causes of vomiting, but the provider must also expand the differential diagnosis to consider extraintestinal etiologies of vomiting, such as sinusitis or pneumonia.

Last, it is important to query adolescent patients about use of alcohol and illicit drugs. Many adolescents may engage in binge drinking, which can lead to acute vomiting. Opioid use has been increasing and may induce vomiting via central effects and by delaying intestinal motility throughout the entire GI tract. As discussed earlier, excessive marijuana use has been clearly shown to induce vomiting. Obtaining a medical history for use of recreational marijuana is becoming increasingly pertinent to pediatric evaluation of vomiting, especially in an era of increasing state legalization and access to marijuana.

PHYSICAL EXAMINATION

The evaluation of vomiting should be targeted to the patient's medical history and physical examination findings. In terms of the latter, the abdominal examination may be the most useful. Bowel obstruction should be considered if the abdomen appears distended or if there are high-pitched bowel sounds (borborygmi) along with a taught abdominal wall. This would require emergent evaluation. Absence of bowel sounds may suggest an ileus. An enlarged liver may suggest a metabolic process.

Growth parameters are an essential part of the physical examination. Weight loss can indicate a more concerning etiology of vomiting, such as an intestinal stricture or pancreatitis. Most causes of vomiting do not result in weight loss.

A thorough neurologic examination should always be performed when examining a child who presents with vomiting. This should include evaluation for papilledema, ataxia, abnormal reflexes, and weakness. Changes in mental status, including lethargy, may be suggestive of increased intracranial pressure, metabolic shock, or an overdose of a toxic substance. Mental status changes can also be seen in IEMs but do not usually occur acutely.

Red Flag Signs and Symptoms

Red flag symptoms that should prompt referral for urgent evaluation include hematemesis (especially with the first episode of vomiting), hematochezia, recurrent bilious emesis, clinical dehydration, evidence of shock, focal neurologic changes, abdominal distention, and absent or tympanic bowel sounds. In addition, it is critical to carefully evaluate vomiting that wakes a child from sleep.

GI CAUSES OF VOMITING

GER and GERD

It is important to distinguish vomiting from "spitting up" in a child with benign gastroesophageal reflux (GER) or pathological gastroesophageal reflux disease (GERD). The former is a common physiologic occurrence in infants who exhibit painless spitting up after feeds but are otherwise growing and developing appropriately. Infants with GER are commonly referred to as "happy spitters" and do not require any acid suppressant therapy. Instead, reassurance should be provided to the family that physiologic reflux will peak at 4 months of age, and almost always resolves by a year of age. Avoiding unnecessary treatments of physiologic GER in infants is part of the *Choosing Wisely* campaign, an initiative of the American Board of Internal Medicine Foundation endorsed by the American Academy of Pediatrics (http://www.choosingwisely.org).

GERD is diagnosed in infants with GER who also have additional troublesome symptoms, such as irritability, poor feeding, or weight loss. These patients may benefit from dietary changes, including exclusion of milk and eggs from the diet of breastfeeding mothers or use of hypoallergenic infant formulas. Infants with GERD may also be treated with gastric acid–suppressing agents, but it is important to recognize that these are helpful for treating irritation or injury related to acid exposure, not for reducing the spitting up.

Constipation

Constipation is one of the most common causes of vomiting through the mechanism of delayed gastric emptying. Symptoms may initially present as nausea and early satiety but can progress to vomiting in more severe cases of fecal impaction. Children can attempt oral medications, but if they are not tolerated, rectal therapy, including suppositories or enemas, may need to be given.

Pyloric Stenosis

One relatively common example of a GI cause of vomiting in newborn infants is pyloric stenosis (PS), which involves a narrowing of the pyloric channel due to a thickening of the pyloric muscle. The incidence of PS is 2 to 3.5 per 1,000 live births and is associated with male sex, age 2 to 7 weeks, being first-born, maternal smoking, preterm delivery, small for gestational age, cesarean delivery, and congenital malformations. (2)

Patients with PS often present with forceful, nonbilious emesis around 1 month of age. Parents often state that their child is "always hungry." A palpable "olive" in the right upper quadrant is considered pathognomic for PS, but an abdominal fluid wave is more frequently seen on physical examination. Failure to thrive, or signs and symptoms consistent with dehydration, should prompt further laboratory and radiologic evaluation.

Initial laboratory evaluation in PS classically reveals a hypokalemic, hypochloremic, metabolic alkalosis. Radiologic evaluation usually begins with ultrasonography. Diagnosis of PS is supported when the thickness of the pyloric muscle is greater than 3 mm and the length of the pyloric channel is greater than 15 mm. (3) An upper GI series can also be obtained to make the diagnosis and is characterized by the finding of a small "trickle" of contrast passing through the pyloric channel.

The initial steps in managing PS include correction of dehydration and correction of any electrolyte imbalances. This should be done before any surgical intervention. Once the child is fully resuscitated, a surgeon typically proceeds with pyloromyotomy.

Gastric Outlet Obstruction

Gastric outlet obstruction is an anatomical abnormality that often presents in infancy. An example of a gastric outlet obstruction is an antral web. In this congenital condition, an upper GI series will suggest an inability of contrast to exit the stomach. More definitive evaluation to diagnose an antral web requires direct visualization via upper endoscopy.

Malrotation with Volvulus

Malrotation with volvulus should always be considered in patients with acute or episodic vomiting, particularly if bilious vomiting is present. During episodes of malrotation with volvulus, older children may cry excessively or complain of severe abdominal pain, and infants may appear limp and lethargic, and meet the clinical criteria for shock. Malrotation can also occur without volvulus and lead to chronic vomiting that is often painless.

The diagnosis of malrotation requires either a barium study to delineate the ligament of Treitz, abdominal ultrasonography, or a computed tomographic scan of the abdomen. An abdominal radiograph obtained during an episode of volvulus usually shows an air-filled, dilated bowel proximal to the level of the obstruction and a paucity of air distal to the obstruction. An upper GI series often reveals an incomplete C sweep of the duodenum, with the small intestine remaining on the right side of the abdomen with failure to cross the midline. Decompression of the intestine with a nasogastric tube followed by emergent surgical consultation is required (Fig 2).

Intestinal Atresia

Intestinal atresia classically presents with bilious emesis in infants within the first few hours of life. Location of atresias along the GI tract may be variable, with abdominal distention often seen with more distal lesions. Intestinal atresia may be associated with a variety of genetic disorders. In particular, duodenal atresia should be investigated in a neonate with trisomy 21 who presents with bilious vomiting and can be diagnosed by a "double bubble" sign on plain film imaging.

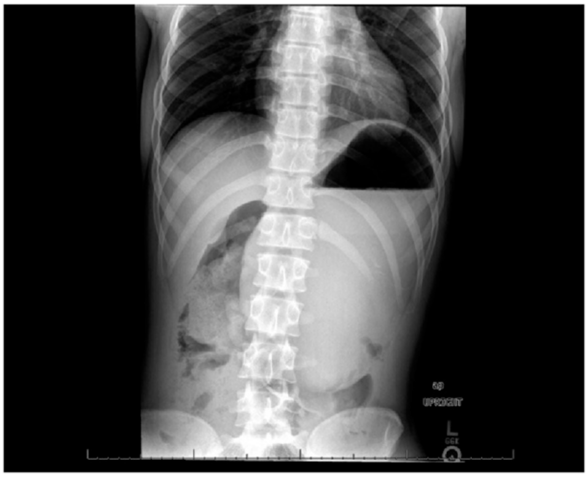

Figure 2. Severely dilated stomach in a patient with intestinal malrotation with volvulus.

Intussusception

Intussusception, or telescoping of the bowel, can occur physiologically. However, if intussusception fails to reduce, it can result in life-threatening obstruction with dilation and necrosis of the bowel. Patients presenting with intussusception are predominantly male, between 3 months and 3 years of age, and have symptoms of abdominal pain and vomiting that begin suddenly and then resolve just as quickly. As with volvulus, these patients can develop bowel ischemia and may appear limp and lethargic, with evidence of shock. Over time, the vomiting can become bilious, and the patient may develop bloody stools. There can also be an appearance of a "red currant jelly" stool, which occurs when blood mixes with mucus.

The mortality rate of discovered intussusception is less than 1%. However, if not identified and treated in a timely manner, intussusception can be fatal. Abdominal ultrasonography is the best method of radiologic evaluation for intussusception, and an air contrast enema can be both diagnostic and therapeutic. Persistent intussusception may require surgical intervention.

Eosinophilic Esophagitis

Eosinophilic esophagitis is a lifelong clinicopathologic inflammatory condition associated with other atopic diseases, with an increasing worldwide prevalence. The emesis in patients with eosinophilic esophagitis is often chronic and is characterized by expulsion of undigested food within a few minutes of eating. Over a lifetime, chronic inflammation due to eosinophilic esophagitis may be associated with fibrostenosis of the mucosa, and esophageal strictures can form. The natural history of eosinophilic esophagitis may explain why older patients will often note dysphagia, particularly with solid foods, whereas younger patients and infants can present with vomiting, food refusal, or failure to thrive.

Eosinophilic esophagitis should be considered in patients with episodic or chronic vomiting and a history of asthma, allergic rhinitis, or eczema. Fluoroscopic examination of the esophagus may reveal a small-caliber or ringed esophagus, as well as stricturing disease (Fig 3). Eosinophilic esophagitis is characterized by various mucosal signs of inflammation that can be noted on upper endoscopy. According to current guidelines, eosinophilic esophagitis must be confirmed by biopsies revealing at least 15 eosinophils per high-power field. (4)

Pancreatitis

Acute and chronic pancreatitis, characterized by inflammation and swelling of the pancreas, can occur for many underlying reasons. Both types can be highly associated with a systemic inflammatory response syndrome, leading to shock and other life-threatening conditions. Necrotizing pancreatitis occurs when the pancreas becomes infected and may present as persistent fever, worsening abdominal pain, and even sepsis. Pancreatitis causes vomiting primarily through inflammatory cytokines, which trigger chemoreceptors. It is important to recognize that an enlarged pancreas can also have a mass effect in the abdomen, leading to obstruction of the duodenum.

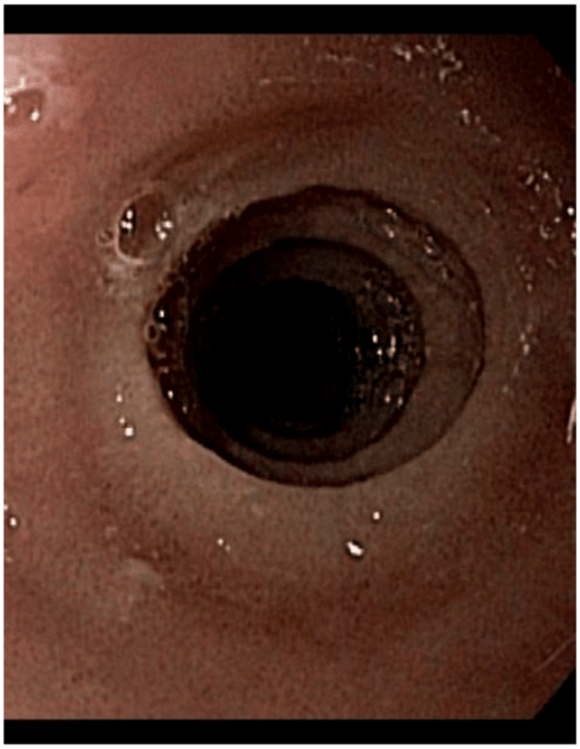

Figure 3. Esophageal stricture in a patient with eosinophilic esophagitis.

Physical examination of patients with pancreatitis often reveals epigastric abdominal pain with radiation to the back. Laboratory evaluation will often demonstrate elevated amylase and lipase levels. Abdominal ultrasonography may be sufficient for diagnosis. However, a computed tomographic scan of the abdomen may be warranted if there is concern for necrotizing pancreatitis.

Gastroparesis

Gastroparesis—a functional delay in stomach emptying—can present with nausea and early satiety. Vomiting secondary to gastroparesis is usually nonbilious and occurs generally at least several minutes after eating. Gastroparesis in children most often follows from viral infections, but the condition is also often idiopathic. (5) Several months may pass before motility of the intestines returns to baseline when gastroparesis follows an infection. There are a variety of other causes of gastroparesis, including type 1 diabetes mellitus, acidosis, and cerebral palsy. Diagnosis is often made by a scintigraphic gastric emptying scan that demonstrates delayed gastric emptying. More formal GI motility testing, including antroduodenal manometry, can also be considered.

Superior Mesenteric Artery Syndrome

Superior mesenteric artery (SMA) syndrome should be considered in a patient with a history of recent weight loss and severe postprandial vomiting. Athletes involved in weight-dependent sports (ie, gymnastics, wrestling, and crew), patients with eating disorders, and those in critical care settings are at particular risk. In SMA syndrome, adipose tissue that normally suspends the SMA over the third portion of the duodenum is reduced. This results in a "nutcracker effect" where the SMA compresses the duodenum, resulting in bowel obstruction.

The best method of evaluation for SMA syndrome is an upper GI series, which may reveal a sharp cutoff sign of contrast that is unable to pass through the duodenum. It may also show a to-and-fro motion of the contrast column. Once identified, resolution of SMA syndrome involves weight gain, which may require bypassing the level of obstruction with a nasal jejunal tube or the use of total parenteral nutrition. Patients may also find it more comfortable to eat while leaning forward.

Intestinal Stricture

Intestinal strictures are rare causes of vomiting and can occur as a complication of various conditions in children. In particular, small-bowel Crohn disease can result in stricturing of the intestine from chronic inflammation; this condition most commonly occurs at the level of the ileum. Patients with intestinal strictures may present with the sudden onset of right lower quadrant abdominal pain and vomiting that improves after a few hours of bowel rest and intravenous fluid resuscitation. An intestinal stricture should also be considered in a patient with a history of intestinal resection with anastomosis or in a patient with a history of necrotizing enterocolitis. In both circumstances, chronic inflammation can lead to the development of fibrotic tissue (Fig 4).

NON-GI CAUSES OF VOMITING

Cyclic Vomiting Syndrome

Considered a migraine variant, CVS is characterized by episodic vomiting spells that present suddenly, occasionally waking a patient in early morning hours, and persist for variable durations, from 1 hour to several days. Many patients with this condition will have a family history of atypical and typical migraine headaches. During episodes, patients are at risk for severe dehydration and may require intravenous fluid resuscitation.

International consensus as outlined in the Rome III criteria for CVS includes stereotypical episodes of vomiting that are acute and last less than 1 week, 3 or more separate episodes in the past year, and absence of any symptoms between episodes.

It is thought that mitochondrial defects or other IEMs may predispose to cyclic vomiting episodes. For these reasons, it is important to inquire about developmental delay and symptoms triggered by certain meal types, such as high-protein meals or prolonged fasting in infants and young children.

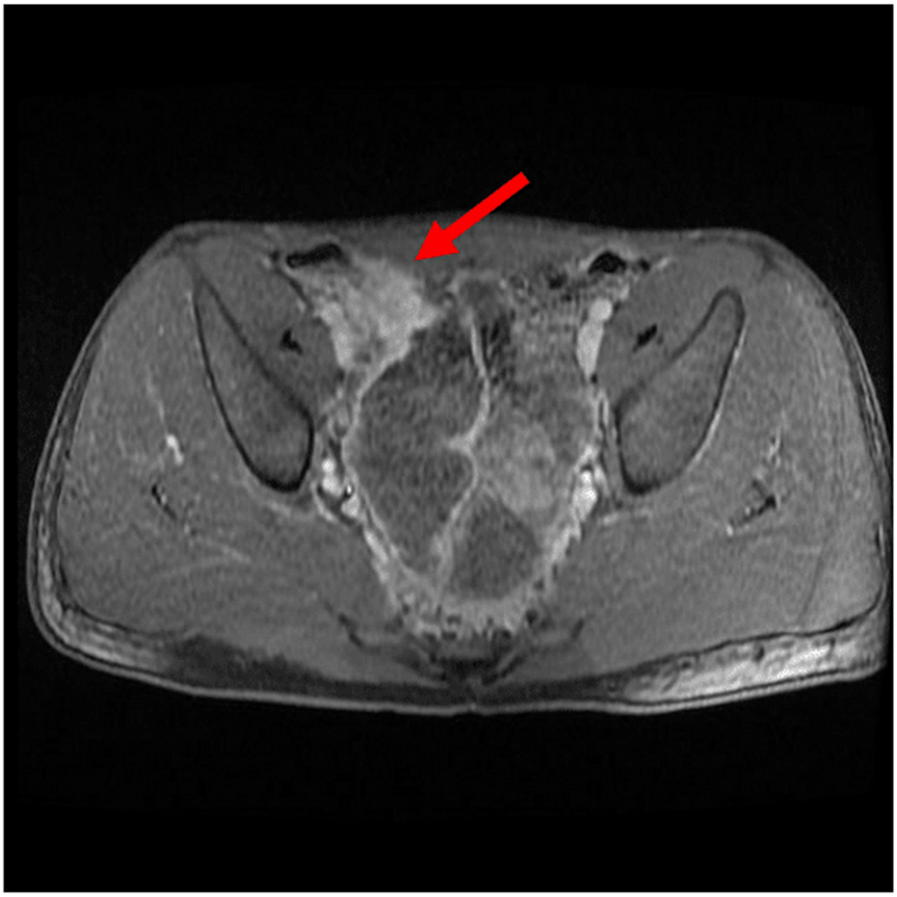

Figure 4. Ileal stricture (arrow) with bowel dilation in a teenager with Crohn disease.

Cannabinoid Hyperemesis Syndrome

This syndrome is an emerging condition associated with chronic marijuana exposure that was first described in 2005 as a mimic of CVS. Although marijuana is generally considered an antiemetic, it is becoming clear that it can also induce a chronic and profound pattern of hyperemesis. Patients with stereotypical CHS have an intriguing hydrophilia, and eliciting a history of seeking hot showers to alleviate vomiting can help differentiate CHS from CVS in teenagers with the condition. Treatment of CHS involves abstinence from marijuana for at least 2 weeks.

Food Protein–Induced Enterocolitis Syndrome

This rare but severe cause of vomiting presents most often during infancy and generally resolves by age 3 years. Although the exact pathophysiology is unknown, FPIES is triggered by non–immunoglobulin E–mediated reactions to the protein component of foods. Unlike immunoglobulin E–mediated food allergy, FPIES often presents 2 to 6 hours after exposure to the offending foods with vomiting and diarrhea, in the absence of respiratory symptoms, swelling, or hives. Foods that are most often implicated as triggers for FPIES include cow milk and soy proteins, as well as glutenin proteins in rice cereal and oatmeal. (6)

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction can cause episodic vomiting due to either intrinsic or extrinsic obstruction of the kidney at the renal pelvis, resulting in hydronephrosis. The resultant dilation of the urinary collecting system and stretching of the renal capsule stimulates vagal afferents through the mechanical pathway to trigger the emetic reflex. Patients with ureteropelvic junction obstruction often present with episodic bouts of vomiting and unilateral flank pain. Their symptoms typically resolve as the obstruction improves. Hydronephrosis noted on ultrasonography during acute episodes that resolves when the child is asymptomatic is highly suggestive of this condition and warrants referral to a pediatric urologist. (7)

Adrenal Insufficiency

The most common cause of adrenal insufficiency is congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Patients with congenital adrenal hyperplasia often present with chronic vomiting and are found to be hyponatremic, hyperkalemic, and hypotensive. Current state-mandated newborn screening generally analyzes for 21-hydroxylase deficiency, which has helped improve detection of this condition before complications occur.

Inborn Errors of Metabolism

Vomiting is a common feature of most IEMs. These conditions include organic acidemias, urea cycle defects, and defects with carbohydrate metabolism such as galactosemia. It is important to have a high index of suspicion for an IEM in patients with vomiting and growth or developmental delay owing to the high morbidity and mortality associated with IEMs.

Increased Intracranial Pressure

One particularly ominous cause of chronic vomiting is increased intracranial pressure, which can occur from either mass effects or pseudotumor cerebri. Vomiting that occurs with positional changes or that causes a patient to wake from sleep should be recognized as red flags for this condition. Increased intracranial pressure may also be associated with other neurologic features, including recurrent and focal headache, difficulties with ambulation, changes in vision or changes in mental status. Findings of the Cushing triad, which includes bradycardia, hypertension, and irregular breathing, should increase suspicion for increased intracranial pressure and prompt urgent evaluation.

EVALUATION OF CHILDREN WITH VOMITING

Laboratory and radiographic evaluation should be based on the characteristic type of vomiting (Table 3). In a pediatric patient with acute vomiting, most laboratory studies will not be helpful in identifying a specific cause of the vomiting but will be important for assessing hydration status. In particular, specific gravity from a urinalysis can be helpful to assess the hydration status of the child, as well as serum electrolyte, blood urea nitrogen, and creatinine levels.

Patients with chronic vomiting are not usually at risk for dehydration. However, evaluation for *Helicobacter pylori* gastritis (urease breath test, *H pylori* stool antigen) should be considered. Non–*H pylori* gastritis or peptic ulcer disease may also be considered with initial screening in appropriate settings by testing stool for occult blood. Occult or visible blood in the stool may also be present with bacterial gastroenteritis and adverse reactions to foods, such as with milk protein allergy.

Inborn errors of metabolism can result in vomiting, but laboratory abnormalities may not be detected unless a patient is acutely ill. For example, a patient with ornithine transcarbamylase deficiency may develop vomiting only after eating a meal high in protein. For that reason, it is important for primary care providers and emergency medicine providers to evaluate for an IEM at the time that vomiting occurs. These laboratory values often include serum amino acids,

TABLE 3. Laboratory and Radiologic Evaluation for Patients with Vomiting by Temporal Pattern

ACUTE	CHRONIC	CYCLIC
Electrolytes (Na+, K+, Cl-)	Electrolytes (Na+, K+, Cl–)	Electrolytes (Na+, K+, Cl–)
BUN	BUN	BUN
Creatinine	Creatinine	Creatinine
Abdominal radiograph	Celiac screen	Glucose
	Amylase	Upper GI series
	Lipase	Serum amino acids
	Urine β-HCG	Urine organic acids
	Hepatic function panel	Urine ketones
	Stool *Helicobacter pylori* antigen	Carnitine profile
	Upper endoscopy	Ammonia
	MRI brain/CT head	Lactate
		Pyruvate
		US abdomen

BUN=blood urea nitrogen, CT=computed tomographic, GI=gastrointestinal, HCG=human chorionic gonadotropin, MRI=magnetic resonance imaging, US=ultrasonography.

urine organic acids, urine ketones, carnitine profile, ammonia, lactate, pyruvate, and a basic metabolic panel.

An upper esophagogastroduodenoscopy (EGD) is an excellent means to evaluate the mucosa of the intestine but almost always requires deep sedation or anesthesia and involves the slight risk of bowel perforation. Endoscopy is most useful to exclude eosinophilic esophagitis, gastritis, peptic ulcer disease, or gastric outlet obstruction as the cause of a child's vomiting. An upper endoscopy may also be necessary to remove a foreign body in the esophagus or stomach that can be the cause of a child's vomiting. Biopsies of the stomach from an EGD can reveal an *H pylori* gastritis not picked up by stool antigen testing. An EGD can also reveal a nodular appearance of the gastric mucosa caused by an *H pylori* infection (Fig 5).

Endoscopy cannot be used to identify malrotation of the intestine or other possible anatomical conditions that can lead to chronic vomiting. The role of upper endoscopy is controversial in suspected CVS. If a child with presumed CVS responds well to medications, and both intracranial pathology and intestinal malrotation are excluded, then it is reasonable to wait to perform an upper endoscopy and to monitor the patient clinically.

Most importantly, endoscopy should never be performed on an unstable child. Fluid resuscitation and electrolyte abnormalities should always be corrected before performing the procedure.

Intestinal manometry represents an emerging modality for evaluating the motility of the intestinal tract in children with vomiting of unclear etiologies. Unfortunately, availability of this technology is limited to larger, tertiary care institutions, and it is often not performed until many other causes of vomiting have been excluded. For example, esophageal manometry may be helpful in evaluating patients with dysphagia when there is concern for achalasia and eosinophilic esophagitis has been excluded.

Limitations of using manometry in children include its invasiveness and poor patient compliance. By definition, a manometry probe must be placed and left in the esophagus for a clinically useful duration of time (generally, 30–90 minutes). The child cannot be put to sleep for the procedure because he or she must be able to swallow on command.

TREATMENT

For most children with vomiting, no treatment is needed. Overtreatment can lead to harm and misdiagnosis. However, in children at risk for dehydration and electrolyte abnormalities, the first steps in managing vomiting should be clinical stabilization with emphasis on the correction of

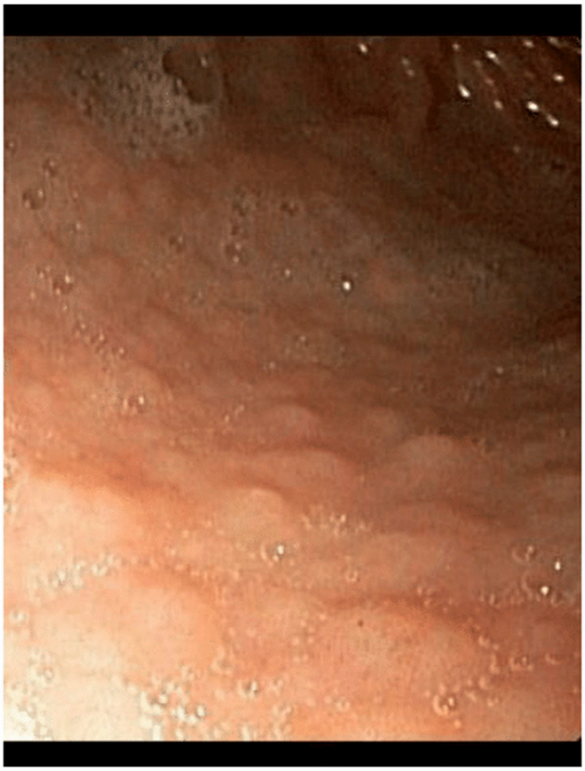

Figure 5. Gastric nodularity due to chronic *Helicobacter pylori* infection.

fluid deficit and electrolyte abnormalities. (1) Often, supportive care with oral or intravenous fluid resuscitation will help relieve vomiting. Identification and correction of the primary problem is obviously the next most important step.

There are several antiemetic medications and a few prokinetic medications that can be considered to minimize vomiting while the etiology is being investigated. Most have poor efficacy and are associated with significant adverse effects. Identifying the underlying pathway that causes a child to vomit is challenging but may be key in selecting a medication that is most likely to be successful. It is important to stress to families that while these medications may decrease episodes of vomiting, the sensation of nausea will often persist.

Table 4 outlines antiemetic medications in accordance with their target receptors and recommended doses. In extreme cases of chronic nausea and vomiting—particularly from chronic gastroparesis—gastric pacing may be considered to relieve symptoms. Gastric pacing is a surgical intervention that involves implanting a pacemaker attached to the external portion of the stomach, with leads that are placed into the intestinal mucosa to stimulate GI motility.

Mechanical

If the cause of vomiting is thought to have a mechanical etiology, such as overdistention of the stomach or a chemotoxin (ie, food poisoning), then antagonists of 5-HT receptors, which are found in the afferent vagal nerves and the CTZ, will be most helpful. Serotonin receptor antagonists include ondansetron, granisetron, dolasetron, and palonosetron. Evidence suggests that the use of ondansetron limits the need for intravenous fluids and hospital admission in pediatric patients with gastroenteritis. (8) Ondansetron has also been shown to be one of the most effective medications in patients receiving chemotherapy and in postoperative induced nausea and vomiting. (9) One of the main adverse effects of ondansetron is diarrhea. It should be used with caution because it can be associated with cardiac arrhythmia (ie, prolongation of the QT interval).

Ginger is also used frequently for chronic nausea and vomiting. Although its mechanism of action is not entirely understood, one of its proposed mechanisms of actions is as a 5-HT_3 antagonist.

Dopamine D_2 receptor antagonists are likely to be most helpful in patients with gastroparesis. Examples of these antagonists include metoclopramide, domperidone, prochlorperazine, and chlorpromazine. The D_2 receptors are found in the CTZ. Unfortunately, the adverse effect profile of D_2 receptor antagonists is significant and can include extrapyramidal reactions. In particular, metoclopramide can easily cross the blood-brain barrier and induce tardive dyskinesia. This has led to a black box warning by the Food and Drug Administration (FDA). Domperidone does not cross the blood brain barrier and does not cause the central nervous system effects seen with metoclopramide.

Blood-borne Toxins

Chemotoxic agents can cause severe vomiting in either an immediate or a delayed fashion. Neurokinin receptor antagonists such as aprepitant and fosaprepitant work by blocking receptors activated by substance P.

To treat vomiting due to chemotoxic agents, it may be most helpful to use serotonin receptor antagonists. These can be used in conjunction with a neurokinin receptor antagonist and dexamethasone for optimal effects. (10)

Motion

Those with motion sickness that affects the vestibular system are most likely to respond to an antihistamine, such as diphenhydramine, cyproheptadine, promethazine, or hydroxyzine. Abdominal migraine syndrome and CVS may also respond to antihistamines, which supports the concept that both conditions are mediated by a common neurologic pathway. Muscarinic receptor blockade, such as

TABLE 4. **Antiemetic Medications and Their Dosages and Target Receptors**

MEDICATION	DOSE	RECEPTOR	NOTES
Ondansetron	0.3–0.4 mg/kg per dose q 4–6 h	5-HT$_3$	Diarrhea is an adverse effect
Granisetron	40 μg/kg/dose q 12 h	5-HT$_3$	
Ginger	250 mg TID	5-HT$_3$ (?)	The mechanism of action of ginger is not completely understood
Cyproheptadine	0.25–0.5 mg/kg per day	5-HT$_{2A}$, 5-HT$_{2B}$, H_1	Stimulates appetite
Amitriptyline	0.25 mg/kg per day (max 1 mg/kg per day)	Serotonin	Increased risk of cardiac arrhythmia
Erythromycin	5 mg/kg per dose q 6 h	Motilin	Can increase risk of pyloric stenosis in infants
Diphenhydramine	5 mg/kg per day divided TID or QID	H_1, D_2	
Promethazine	0.25–1 mg/kg per dose q 4–6 h	H_1	Contraindicated in children <2 y old due to respiratory depression
Meclizine	25–50 mg 1 h before travel	H_1	For patients 12 y and older
Prochlorperazine	5–10 mg q 6–8 h (≥40 kg)	D_1, D_2	
Metoclopramide	0.1–0.2 mg/kg per dose q 6–8 h	D_2	Black box warning: increased risk of tardive dyskinesia
Scopalamine	1 mg transdermal disc applied behind ear q 3 d	M_1	
Aprepitant	Children 6–30 kg: 3 mg/kg on day 1, then 2 mg/kg on days 2 and 3 Children >30 kg: 125 mg on day 1, then 80 mg on days 2 and 3	NK_1	Indicated for chemotherapy-induced nausea Causes fatigue, dizziness Not for long-term use

5-HT=5-hydroxytryptamine, q=every, QID=4 times per day, TID=3 times per day.
From Li BUK. Nausea, vomiting, and pyloric stenosis In: Kleinman RE, Goulet O, Meili-Virgani G, et al, eds. Walker's Pediatric Gastrointestinal Disease; *adapted from both the 5th (2008) and 6th (2018) editions; used with permission from PMPH USA Ltd, Raleigh, NC.*

scopolamine, is also effective prophylactically in treating patients with motion sickness. Scopolamine is administered as a transdermal patch.

Emotional Response

Patients with emotional triggers of vomiting are most likely to benefit from cognitive behavioral therapy and biofeedback.

SPECIAL CIRCUMSTANCES

Bilious Emesis in Infants

Bilious emesis is *never* acceptable in a neonate and should always be concerning for intestinal obstruction. The level of the obstruction cannot be differentiated based on bilious emesis itself. It can represent a proximal obstruction such as duodenal atresia or a distal obstruction such as Hirschsprung disease. Abdominal distention usually represents a more distal bowel obstruction.

The first step in managing a neonate with presumed bowel obstruction is decompression with a nasogastric tube. This should be followed by correction of dehydration and any electrolyte abnormalities.

An abdominal radiograph can help localize the obstruction. Follow-up with an upper GI series with or without a small-bowel follow-through is often warranted. However, if Hirschsprung disease is suspected, a contrast enema is the preferred study. Ideally, an unprepped contrast enema is most helpful so as not to obscure the transition line. A CT scan of the abdomen can evaluate the entire intestine quickly but carries a higher radiation exposure than contrast imaging.

Projectile Vomiting

As with bilious emesis, projectile or forceful vomiting should always be evaluated carefully. Projectile vomiting can be seen in cases of PS, gastric outlet obstruction, or even increased intracranial pressure. Concerns about conditions associated with projectile vomiting have been widely spread in parenting literature, and families will often use the term indiscriminately. As the clinician, it may be helpful to ask a parent to identify where in the room the vomitus would land with the patient sitting in the parent's lap to determine whether the description matches the symptom.

WHEN SHOULD YOU REFER?

Referral for vomiting—acute, chronic, or cyclic—may be appropriate when symptoms are persistent and the cause of vomiting cannot be established. Specialists who may be useful for diagnosing and managing persistent or chronic vomiting in children include gastroenterologists, neurologists, endocrinologists, metabolic specialists, and surgeons, depending on the presumed pathway. Regardless of the underlying cause, it is also critical for primary care physicians to recognize signs and symptoms of dehydration and shock and to refer them to emergency departments for urgent rehydration and stabilization.

Summary

- Vomiting is a common symptom of a myriad of conditions that can cause tremendous stress for the child and caregivers. Finding an etiology can be challenging because vomiting can involve a variety of different organ systems in the body.
- There are 4 main physiologic pathways that can trigger the emetic reflex: mechanical, blood-borne toxins, motion, and emotional triggers. (1) Each pathway is triggered by different organ systems and involves different neurotransmitters.
- Establishing a differential diagnosis for vomiting should take into account both a child's age and temporal characteristics of their vomiting.
- Based on strong research evidence, (1) the first step in management should be correction of dehydration or any electrolyte abnormalities, as well as decompression if there is concern for a bowel obstruction.
- It is critically important to recognize red flag signs and symptoms that may suggest more life-threatening causes of vomiting, including nocturnal vomiting that awakens the patient from sleep, weight loss, hematemesis, severe abdominal distention, mental status changes, and bilious emesis, particularly in a neonate.

References for this article are at http://pedsinreview.aappublications.org/content/39/7/342.

PIR Quiz

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1. A 17-year-old developmentally appropriate boy comes to the clinic for evaluation of vomiting. He reports that he has had episodes of nausea with nonbloody, nonbilious emesis on awakening. These episodes occurred 2 to 3 times each week, mostly over weekends for the past 2 months. He denies any abdominal pain, diarrhea, weight loss, fever, or difficulty swallowing. His vomiting never causes him to awaken from sleep. There is no family history of migraine headaches. Results of physical examination, including abdominal and neurologic examinations, are normal. Which of the following is the most likely possible explanation of this patient's symptoms that needs further investigation?
   - A. Adrenal insufficiency.
   - B. Inborn error of metabolism.
   - C. Intestinal malrotation with volvulus.
   - D. Intussusception.
   - E. Marijuana use.
2. A 4-month-old boy is seen for a health maintenance visit. Since his 2-month health maintenance visit he has been doing well and has not had any major problems except for episodes of spitting up after feedings. These episodes have worsened in the past few weeks and occur after every feed. There is no history of fever, runny nose, cough, rashes, or diarrhea. The baby was exclusively breastfed until a month ago when mom returned to work. He is currently on human milk supplemented with cow milk–based formula. He is a good eater and takes 6 oz of formula every 3 to 4 hours with breastfeeding in between 3 to 4 times a day. On physical examination, his height and weight are on the 90th percentile for age. The results of his physical examination are normal. Which of the following is the next best step in the management in this patient?
   - A. Esophageal manometry.
   - B. Ph probe.
   - C. Reassurance.
   - D. Switch to a soy-based formula.
   - E. Upper endoscopy.
3. A 6-week-old baby boy is brought to the emergency department (ED) by his parents because of recurrent episodes of emesis. The vomiting started 2 weeks ago but worsened during the past 10 days. The parents describe the emesis as "forceful" and "shooting" and lately occurring after every feed. The baby has had no fever or diarrhea, no decrease in activity, and seems hungry all the time. He was noted today to be more sleepy than usual and has had a decrease in wet diapers in the past 24 hours, which prompted the ED visit. On physical examination, the baby is sleepy but arousable. His weight is unchanged from his last visit at 4 weeks of age. Physical examination is significant for tachycardia, dry mucous membranes, and a sunken anterior fontanelle. Abdominal examination shows a nondistended, nontender abdomen with sluggish bowel sounds. Which of the following is the best immediate next step in the management of this patient?
   - A. Abdominal ultrasonography.
   - B. Correction of dehydration and electrolyte imbalances.
   - C. Start oral ondansetron therapy.
   - D. Upper endoscopy and biopsies.
   - E. Upper gastrointestinal and small-bowel follow-through.

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4. A 10-year-old boy is brought to the clinic by his parents. He frequently becomes nauseous when going on car rides longer than 1 hour. From the following list of medications that are used for vomiting, which is not likely to improve his symptoms?
   - A. Cyproheptadine.
   - B. Diphenydramine.
   - C. Ondansetron.
   - D. Promethazine.
   - E. Scopalamine.
5. You are called by the newborn nursery nurse because a 1-day-old girl had an acute episode of bilious emesis. The baby is being breastfed. There is no history of fever. The baby passed meconium but has no diarrhea. On physical examination, the abdomen is soft and mildly distended. Which of the following is the most appropriate next step in the management of this patient?
   - A. Perform abdominal ultrasonography.
   - B. Perform an upper endoscopy.
   - C. Place a nasogastric tube.
   - D. Reassurance and continued observation.
   - E. Switch the baby to an elemental formula.

Index of Suspicion

1 Microcephaly, Skeletal Dysplasia, and Immunodeficiency in a Newborn

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EDITOR'S NOTE

The editors of *Pediatrics in Review* greatly appreciate feedback from readers, many of whom made it clear that reading the case reports in print form is still preferred. So, in response to your input, this issue takes us "back to the future" with all *Index of Suspicion* cases again appearing in the print journal as well as online. Thanks for reading, and thanks for the feedback!

Philip R. Fischer, MD
Associate Editor, *Index of Suspicion*

PRESENTATION

A newborn is admitted to the NICU for evaluation given abnormal prenatal ultrasonography findings of small for gestational age and shortened long bones. He was born at 39^{+1} weeks' gestation to a nonconsanguineous, healthy, 32-year-old gravida 2, para 1 mother and a healthy 33-year-old father by elective cesarean delivery. The pregnancy and labor were normal. No invasive testing was performed prenatally. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively.

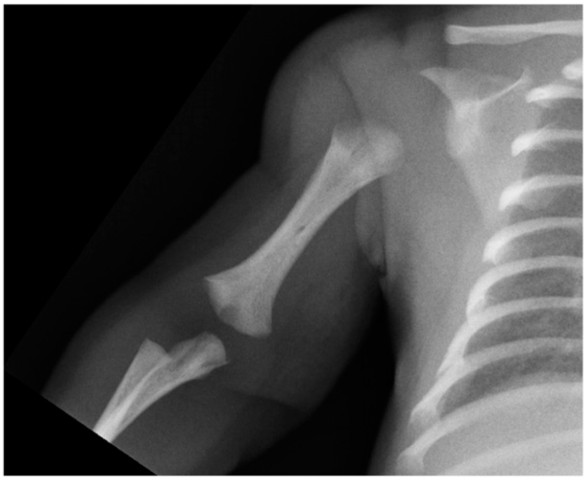

Figure 1. Radiograph of the patient's right arm showing relative shortening of the humerus.

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Dr Belal and Ms Malcolmson have disclosed no financial relationships relevant to this article. Dr Day-Salvatore has disclosed that she receives research grant funding for longitudinal studies from Sanofi Genzyme and grant funding from the New Jersey Department of Health Special Child Health and Early Intervention Services. She also serves as a lysosomal storage disease expert for Sanofi Genzyme and receives travel reimbursement and honoraria from the company. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

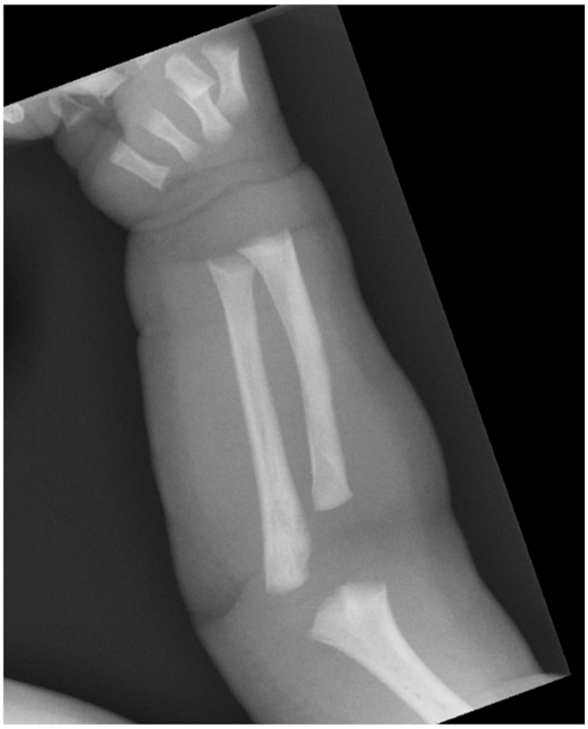

Figure 2. Radiograph of the patient's left forearm. Note the distal metaphyseal cupping of the radius and ulna.

The maternal family history is remarkable for endometrial cancer in the grandmother and mesothelioma and prostate cancer in the great-grandfather. A paternal great-aunt had breast cancer and the paternal great-grandmother had ovarian cancer. The couple has a healthy 3-year-old daughter. Physical examination is notable for head circumference of 31.5 cm (<3rd percentile), weight of 2,955 g (16th percentile), length of 47.5 cm (18th percentile), mild shortening of proximal long bones more notable in upper than lower extremities, and shortening of digits. Physical examination findings are otherwise normal. Skeletal survey radiographs show rhizomelic shortening of long bones (Fig 1), metaphyseal cupping of the proximal humeri, distal femora, radii, ulni (Fig 2), tibulae and fibulae, trident acetabula (Fig 3), and hypoplastic metacarpals (Fig 4). The state newborn screen returns positive for severe combined immunodeficiency (SCID) later classified as leaky SCID with further lymphocyte studies. A spondyloepimetaphyseal dysplasia gene sequencing panel shows a pathogenic mutation in the *FGFR3* gene, which is associated with achondroplasia. However, because the findings of microcephaly and SCID are not consistent with achondroplasia, and neither are the radiographs and physical examination findings pathognomonic, whole exome sequencing is performed, which reveals the diagnosis.

DISCUSSION

Whole exome sequencing confirmed a de novo pathogenic mutation in the *FGFR3* gene, which is associated with achondroplasia and homozygous variants in the *NBN* gene, which is associated with Nijmegen breakage syndrome (NBS).

Achondroplasia is an autosomal dominant skeletal dysplasia caused by mutations in the fibroblast growth factor receptor 3 gene (*FGFR3*). It is characterized by macrocephaly, short stature, shortening of arms and legs, brachydactyly, kyphoscoliosis, and lumbar lordosis.

Nijmegen breakage syndrome is a rare autosomal recessive chromosomal instability syndrome caused by pathogenic variants in the *NBN* gene located at chromosome 8q21.3. It is characterized by microcephaly, growth restriction, immunodeficiency, radiation sensitivity, and predisposition to malignancy.

MASKING OF BOTH CONDITIONS

The newborn did not exhibit the classic clinical signs of achondroplasia such as macrocephaly, depressed nasal bridge, frontal bossing, and narrow chest; however, he presented with moderate microcephaly (head circumference of 31.5 cm), which is also not typical of patients with NBS who classically have severe microcephaly at birth. This is an example of how the presence of 2 genetic conditions can mask the classic clinical findings of each other.

PATHOPHYSIOLOGY

The protein product of the *NBN* gene is nibrin, which plays a key role in regulating the activity of protein complexes that are involved in end-processing of normal and mutated DNA double-strand breaks generated by ionizing radiation. If DNA double-strand breaks are not repaired, they result in genomic instability, gene mutations, or chromosome rearrangements that can lead to cancer. (1) Nibrin also plays a role in lymphocyte maturation and immunoglobulin class switching. (2)

EPIDEMIOLOGY

Although NBS is a rare disease, its incidence rates are increasing given advances in technology and increased awareness of the condition. The highest prevalence is in patients with eastern European ancestry, particularly from Poland, Slovakia, and Czech Republic. (3) Our patient's father is of Slovakian and mixed European descent, and his mother is of mixed European ancestry.

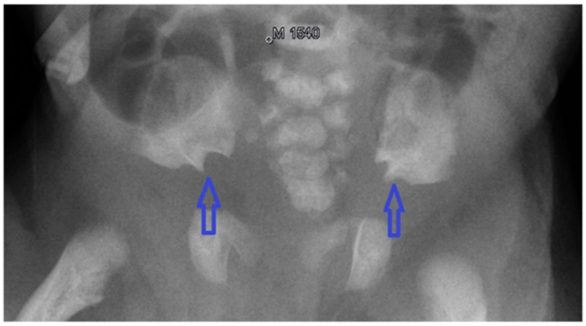

Figure 3. Radiograph of the patient's pelvis. Arrows pointing at the trident acetabula.

THE HOMOZYGOUS PATIENT

Nijmegen breakage syndrome is an autosomal recessive disease, hence it necessitates the inheritance of 2 copies of pathogenic variants in the *NBN* gene to manifest.

The main clinical finding in infants with NBS is severe progressive microcephaly that is present at birth. Head circumference is usually 10 to 12 cm less than the mean. (4) It is associated with mild-to-moderate intellectual disability and decline in cognitive skills; however, gross motor development is typically not affected. Patients may be appropriate or small for gestational age at birth, then they develop growth restriction over the first 2 years after birth, followed by normal growth velocity. Given the period of initial growth delay, adult height is typically within the lower normal range. Children with NBS have characteristic facial features, including upslanting palpebral fissures, sloping forehead, prominent midface, long nose, and receding mandible. Some patients with NBS also develop cutaneous findings, such as café-au-lait macules, hypopigmented skin lesions, and cutaneous noncaseating granulomas. (5)(6)

Cancer is the most common cause of death in patients with NBS, with lymphoma and leukemia accounting for most. The increased risk of cancer is due to chromosomal instability and sensitivity to ionizing radiation. (7)

Patients with NBS have a reduced number of B and T lymphocytes, resulting in defective humoral and cellular immunity, with sinopulmonary infections being the most common, which can result in bronchiectasis and chronic lung disease. Patients may have low T-cell receptor excision circles (TRECs) due to low T-lymphocyte count at birth; therefore, in states where a TREC assay is performed as part of newborn screening, a positive screen for SCID may be the first presentation of NBS. (8)

THE HETEROZYGOUS PATIENT

Heterozygous carriers of pathogenic variants in the *NBN* gene are typically asymptomatic; however, they have an increased risk of developing cancer over their lifetime, particularly breast and prostate cancer. (9) Our patient has a significant family history of cancer, which may be attributed to the pathogenic variants in *NBN* gene. The patient's sister, mother, father, maternal grandmother, and 2 great-aunts tested positive for the familial pathogenic variant in *NBN*.

TREATMENT AND PROGNOSIS

There is no specific treatment for NBS. Intravenous immunoglobulin is given if immunoglobulin levels are low, and antibiotic prophylaxis should be instituted. Live vaccines must be avoided.

Our patient's mother was advised to avoid breastfeeding due to a risk of cytomegalovirus transmission (which can be potentiality life-threatening in immunocompromised patients) and to use trimethoprim-sulfamethoxazole and fluconazole for prophylaxis of *Pneumocystis jiroveci* pneumonia and disseminated candidiasis, respectively. Intravenous immunoglobulin treatments were also administered within the first month after birth due to the defective humoral immune system.

Household members of patients with combined humoral and cell-mediated immunodeficiencies such as

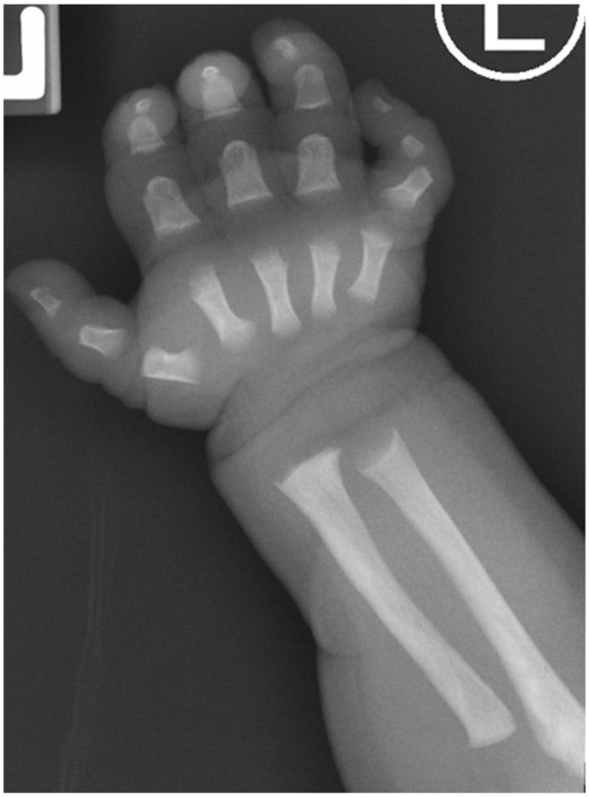

Figure 4. Radiograph of the patient's right wrist. Note the relatively short length of the metacarpal bones.

NBS are encouraged to receive all vaccinations, including live vaccines, according to schedule except for the oral polio vaccine (which is no longer available in the United States at the time of this writing; however, it is still available in many countries worldwide) due to the potential risk of shedding the virus in the stool and infecting the immunocompromised individual. (10) The Infectious Diseases Society of America also advises against administering the live attenuated influenza vaccine to household contacts of a patient with SCID and individuals who live with an immunocompromised hematopoietic stem cell transplant recipient within 2 months after the transplant. (10)

Parents and primary care providers of patients with NBS should be aware of the increased cancer risk. Prompt investigation should be initiated if patients develop symptoms. All forms of ionizing radiation, such as radiographs or computed tomographic scans, must be avoided unless absolutely necessary.

Patients with NBS are very sensitive to radiation treatment and chemotherapy; therefore, if they develop malignancy, the radiation dosage should be limited. (11) Hematopoietic stem cell transplant has been successfully used in some patients who developed severe immunodeficiency or cancer. Our patient's older sister is a human leukocyte antigen (HLA)–compatible donor; however, the risks associated with hematopoietic stem cell transplant outweigh the benefits at this time. (12)

Patients with NBS have a reduced life expectancy due to the early onset of malignancies. The International Nijmegen Breakage Syndrome Study Group estimates the age at death to range from 2 to 21 years. (7)

Lessons for the Clinician

- Physicians should be aware that an individual may have more than 1 genetic condition and that the clinical manifestation of 1 condition can mask or alter the presentation of the other.
- Clinicians should be aware of the clinical features of Nijmegen breakage syndrome (NBS) and realize that an abnormal newborn screen for severe combined immunodeficiency along with microcephaly can be the initial presenting features of NBS.
- Clinicians should understand that NBS is associated with cancer risks in both homozygotes and heterozygotes.

References and for this article are at http://pedsinreview.aappublications.org/content/39/7/359.

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3-month-old Boy with Micropenis

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AUTHOR DISCLOSURE Dr Tosur has disclosed no financial relationships relevant to this article. Dr Karaviti has disclosed that her husband is founder and CEO of Vivante Health. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 3-month-old previously healthy boy was referred to Endocrinology for evaluation of a micropenis. Small phallic size was first noted by a pediatrician at his 2-week-old health maintenance visit. He is feeding well, making good wet and stool diapers. There is no history of any episodes concerning for hypoglycemia. There was no problem during the pregnancy, during delivery, or after birth. The mother denied smoking, consuming alcohol, medication use, or diabetes during pregnancy. He was born at 40 weeks of gestation via vaginal delivery. The birthweight was 3,544 g. He is not taking any medications. His development is appropriate for his age. There is no family history of male infertility, genital ambiguity, or sudden infant death syndrome. Physical examination reveals a weight and height between the 5th and 15th percentile, a high-arched palate, and mild low-set ears. Review of his previous growth charts showed that his weight was at the 65th percentile at birth, the 30th percentile at 2 weeks of age, and the 23rd percentile at 2 months of age and his height was at the 88th percentile at 2 weeks of age and the 68th percentile at 2 months of age. His stretched penile length is 2 cm with a breadth of 0.7 cm. The urethral opening is in a normal position. The scrotum is well rugated with hyperpigmentation and bilaterally descended testicles. Further blood work and imaging reveal the diagnosis.

DISCUSSION

He underwent pituitary hormonal screenings, including tests for thyroid function, growth factors, and adrenocorticotropic hormone stimulation, and all the results were normal. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone were undetectable. Antimüllerian hormone and inhibin B levels were normal. Hence, he was diagnosed as having isolated hypogonadotropic hypogonadism. Magnetic resonance imaging of the brain showed normal anatomy of the pituitary, but the olfactory bulbs were bilaterally absent (Fig 1). Hypogonadotropic hypogonadism and absent olfactory bulbs were consistent with Kallmann syndrome. Genetic testing was ordered. He was started on 25 mg of intramuscular testosterone monthly for 3 months to induce penile growth. Response to the treatment will be assessed after the third injection.

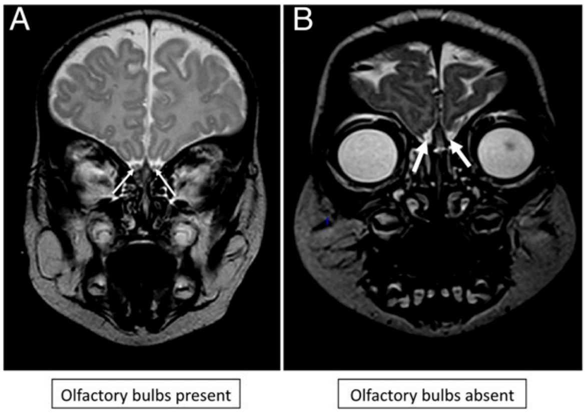

Figure 1. A. A patient with intact olfactory bulbs (thin arrows). B. Our patient with absent olfactory bulbs (thick arrows). (Images courtesy of Dr Jill Hunter.)

Definition and Pathogenesis of Micropenis

Micropenis is defined as a penile length less than 2.5 SD below the mean value for a given age (eg, <2.5 cm for a term baby). Micropenis is mainly caused by deficient fetal testosterone secretion or action. Although hypogonadotropic hypogonadism and primary hypogonadism result in decreased or absent testosterone secretion, the effects of testosterone require binding to a normal androgen receptor, 5α-reductase activity to produce dihydrotestosterone, and growth hormone to act synergistically with testosterone to induce penile growth. Thus, a comprehensive evaluation is crucial for diagnosis and management.

The male external genitalia develops from undifferentiated genitalia between 8 and 12 weeks of gestation (Fig 2). Testicular descent and the penile length depend on testosterone production, which is primarily regulated by human chorionic gonadotropin secreted by the placenta until 15 to 20 weeks of gestation, and pituitary gonadotropins (mainly LH) afterward. (1) Also, FSH is important for sertoli cell development and spermatogenesis. (2)

The Condition

Kallmann syndrome is an inherited disorder characterized by hypogonadotropic hypogonadism and anosmia (partial or complete). (3) This is the most common form of gonadotropin deficiency. The molecular pathogenesis includes impairment of olfactory axon development and gonadotropin-releasing hormone neuron migration. (4) It was named after Dr Franz Josef Kallmann, who described the syndrome in 1944. (3) There are at least 17 known genes associated with Kallmann syndrome. (5) Consistent signs and symptoms include micropenis and undescended testicles in boys, infantile ovaries and uterus in girls, and lack of spontaneous puberty and infertility in both sexes. Aplasia or hypoplasia of the olfactory bulbs and a loss of the sense of smell may occur. Very rarely, patients also have unilateral renal

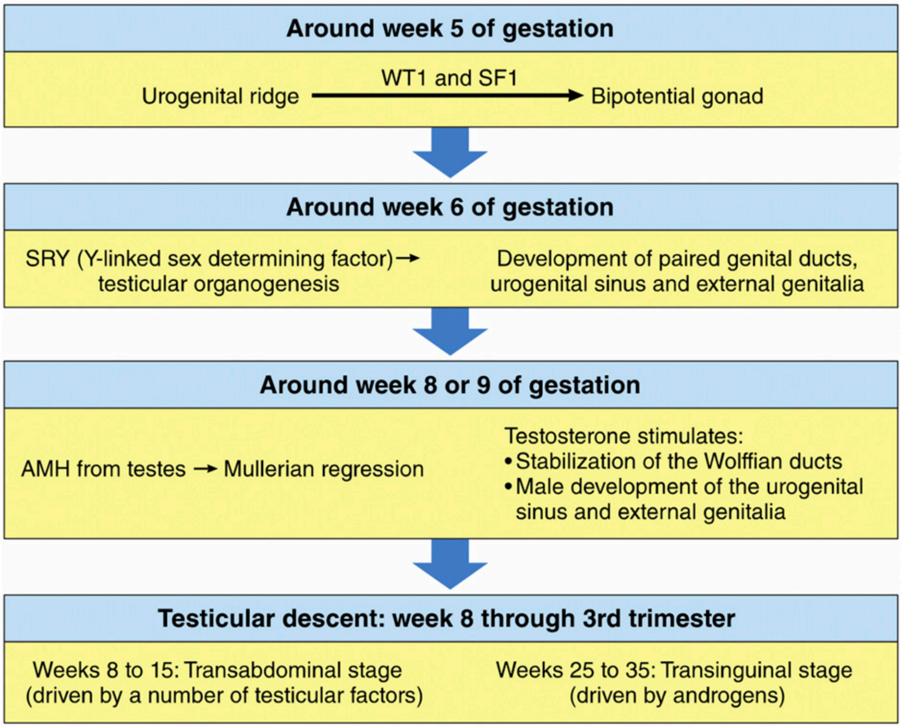
Around week 5 of gestation
Urogenital ridge
WT1 and SF1
Bipotential gonad
Around week 6 of gestation
SRY (Y-linked sex determining factor)→ testicular organogenesis
Development of paired genital ducts, urogenital sinus and external genitalia
Around week 8 or 9 of gestation
AMH from testes → Mullerian regression
Testosterone stimulates:
• Stabilization of the Wolffian ducts
• Male development of the urogenital sinus and external genitalia
Testicular descent: week 8 through 3rd trimester
Weeks 8 to 15: Transabdominal stage (driven by a number of testicular factors)
Weeks 25 to 35: Transinguinal stage (driven by androgens)

Figure 2. Timing of gonadal determination and differentiation. AMH=antimüllerian hormone.

agenesis, cleft lip and palate, and neurologic problems, including synkinesia (mirror movements), sensorineural deafness, eye movement abnormalities, and mental retardation. (4) Some patients may have color blindness.

Diagnosis

The diagnosis can be made by confirming hypogonadotropic hypogonadism and anosmia. (3) The minipuberty of infancy (up to 6 months in boys and 2–3 years in girls) provides a window of opportunity for confirming hypogonadotropic hypogonadism by demonstrating low sex hormones (testosterone/estradiol) with low LH/FSH. (6) Magnetic resonance imaging of the brain is helpful in identifying aplasia or hypoplasia of the olfactory bulbs and confirming the normal pituitary anatomy. Recognition of smell is a developmental milestone, and odor identification is not reliable in children younger than 6 years. (7) Formal smell testing is the best way to confirm partial or complete anosmia because patients may not be aware. The diagnosis of Kallmann syndrome can also be established in the context of hypogonadotropic hypogonadism and hypoplastic/aplastic olfactory bulbs. A genetic etiology can be identified via genetic testing (hypogonadotropic hypogonadism panel). (8) It is very important to screen patients with hypogonadotropic hypogonadism for other pituitary hormone deficiencies because it can be isolated or a part of hypopituitarism. This can identify a medical emergency in the case of central adrenal insufficiency.

Management

After the diagnosis, patients should be screened for potential associated conditions. Renal ultrasonography, audiology screening, and formal smell testing (if age appropriate) should be considered. (4) Micropenis in males should be managed with a 3-month course of monthly testosterone treatment, (6) preferably within the first 6 months after birth. Cryptorchidism may require orchiopexy if testicles are not descended by 1 year of age. Once they reach 12 to 13 years of age, both boys and girls require pubertal induction with sex steroids for the development of secondary sexual characteristics, skeletal maturation, and pubertal growth spurt. There are also viable options for fertility in these patients with appropriate treatment regimens, including long-term gonadotropin-releasing hormone administration or subcutaneous gonadotropin injections. (5) Establishing the diagnosis early is key for a patient to develop along with his or her peers. These interventions will enable appropriate penile growth in infancy for males, pubertal induction in adolescence, and fertility in adulthood.

Follow-up

Our patient completed a 3-month course of intramuscular testosterone injections. The stretched penile length was measured as 3.5 cm a month after his completion of testosterone treatment. The genetic testing revealed that he is heterozygous for the c.92-19G>A variant of uncertain significance in the *FGFR1* gene. He was referred to Genetics for genetic counseling and parental genetic testing.

Lessons for the Clinician

- Hypogonadotropic hypogonadism should be considered in cases of micropenis.
- In the context of micropenis, hypopituitarism should be excluded because central adrenal insufficiency might be a medical emergency.
- It is important to determine whether hypogonadotropic hypogonadism is isolated or associated with a genetic defect, structural abnormality, or particular syndrome.

References for this article are at http://pedsinreview.aappublications.org/content/39/7/363.

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3

Skull Depression in a 9-month-old Girl

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AUTHOR DISCLOSURE Drs Galvis, Shoo, and Shedlock have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 9-month-old unvaccinated African American girl presents to the emergency department for the evaluation of an abnormal head "bump." The mother reports that 5 days before presentation the patient rolled over off a bed and fell 3 feet to the ground. After the fall the girl exhibited no behavioral changes, apparent pain, or emesis. Since the incident, the mother reports that the patient has been doing well, although she became concerned 2 days ago when she noticed a depression on her daughter's head while bathing her.

The infant was born full term but small for gestational age. The mother reports no complications with the birth but that a radiograph was obtained in the nursery showing bilateral "bowed legs." However, the patient was lost to follow-up after nursery discharge with no establishment of a primary care physician.

On examination in the emergency department, her vital signs are as follows: temperature, 98°F (36.7°C); heart rate, 156 beats/min; respiratory rate, 34 breaths/min; and oxygen saturation, 98% on room air. The patient's weight and height are both below the third percentile. The patient is interactive and playful. There is a small depression 1.6 in (4 cm) in diameter on the left parietal region of her head, with no crepitus or tenderness to palpation. The remaining physical examination findings are normal except for yellowish translucent teeth.

Laboratory studies are obtained and show a complete blood cell count and complete metabolic profile within normal limits. A head computed tomographic scan without contrast illustrates a 13-mm depressed comminuted left parietal skull fracture with possible small underlying subarachnoid hemorrhage (Fig 1). Additional imaging and laboratory evaluation lead to the diagnosis.

DISCUSSION

A skeletal survey obtained in the emergency department showed multiple fractures, including a "ping-pong" type of fracture of the posterior left parietal bone (Fig 2), a healed deformity of the proximal left femoral shaft (Fig 3), slight loss of height of the midthoracic vertebral bodies, and diffuse bone undermineralization. Trauma surgery was consulted, and Child and Protective Services was called for suspicion of nonaccidental trauma (NAT). The patient was admitted to the PICU for monitoring, where ophthalmologic examination findings were negative for retinal hemorrhages.

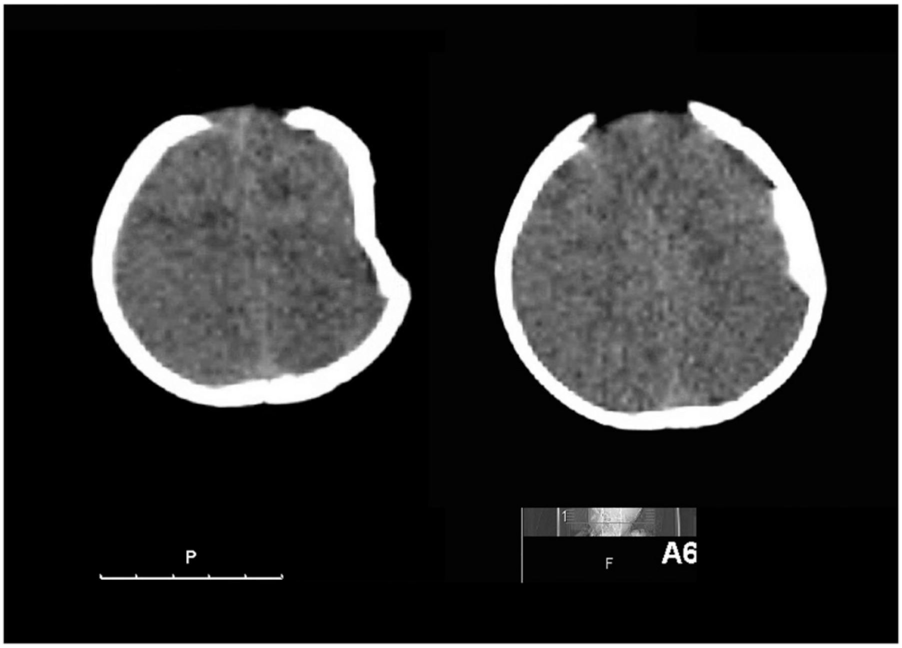

Figure 1. Computed tomographic scan illustrates a 13-mm depressed comminuted left parietal skull fracture with possible small underlying subarachnoid hemorrhage.

The mother, on further questioning, reported that the father of the child has a history of fractures due to minor trauma. An extensive review of the patient's newborn records showed that prenatal ultrasonography was concerning for a possible congenital bone disorder. An endocrinologist and a geneticist were consulted; both recommended additional laboratory tests for further evaluation. Growth hormone markers insulin-like growth factor-1 and insulin-like growth factor binding protein 3, thyroid studies, a celiac panel, erythrocyte sedimentation rate, complete metabolic profile, prealbumin level, and genetic testing for osteogenesis imperfecta (OI) targeting the genes *COL1A1* and *COL1A2* were ordered. During the hospital stay, all the laboratory test results were normal, with the genetic study results pending. Orthopedic surgery and neurosurgery cleared the patient for discharge without the need for further intervention. She was discharged to her maternal grandmother, with Child and Protective Services closely following her while the genetic evaluation was pending. A month after discharge the genetic results confirmed the diagnosis of OI with a point nucleotide mutation of guanine to thymine in exon 17 of the *COL1A2* gene (converting glycine to cysteine). This mutation has not been previously reported, so disease severity cannot be predicted.

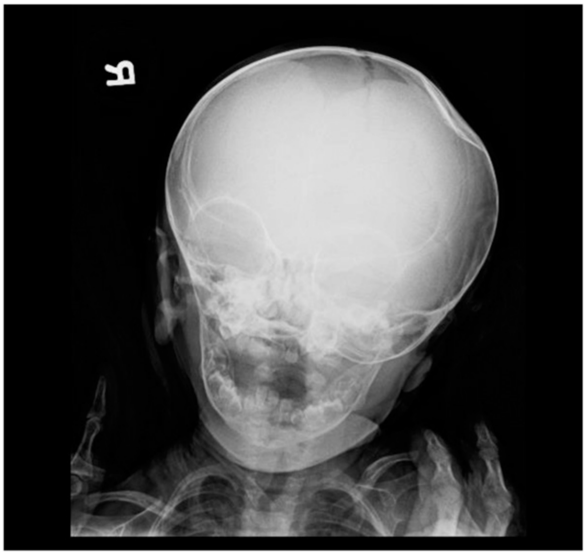

Figure 2. Skeletal survey shows a "ping-pong" type of fracture of the posterior left parietal bone.

Differential Diagnosis

The differential diagnosis for OI includes NAT and a variety of skeletal conditions associated with bone deformities, such as hypophosphatasia and rickets. The appearance of multiple fractures in various stages of healing can make distinguishing NAT from OI very difficult. Information that may lead the clinician toward a diagnosis of OI includes a positive family history, poor growth, born small for gestational age, hearing loss, dentinogenesis imperfecta, long bone deformity, and/or blue sclera. (1)(2)

Although the birth history made a congenital bone disease concerning, the delayed emergency department

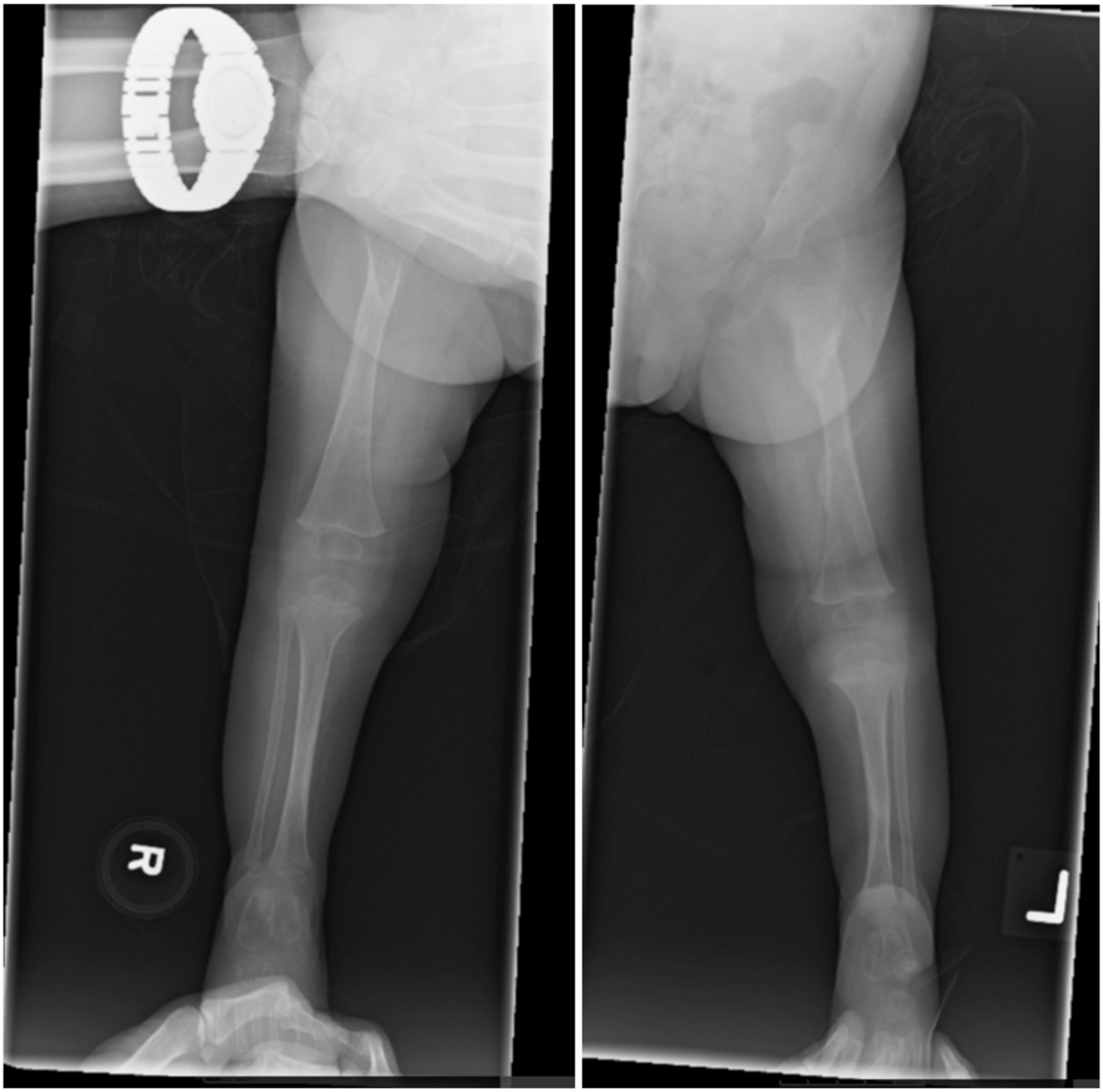

Figure 3. Skeletal survey shows a healed deformity of the proximal left femoral shaft.

presentation, lack of an outpatient pediatrician, and unvaccinated status raised the suspicion for NAT. It is important to note that some studies estimate that a child is 24 times more likely to have a fracture caused by NAT than from OI. (3) Hypophosphatasia, unlike OI, causes decreased serum alkaline phosphatase levels, but this patient had normal serum levels. Rickets can cause growth retardation, abnormal tooth formation, defective bone mineralization, and elevated alkaline phosphatase similar to OI. However, rickets has specific radiographic findings, including widening of the epiphyseal plates, metaphyseal cupping, looser zones, and rachitic rosary. In this case, a clinical diagnosis of OI was made when considering the history, imaging, laboratory, and clinical findings (especially the yellow translucent teeth), which was later confirmed with genetic testing.

The Condition

Osteogenesis imperfecta is a rare disorder that occurs at a rate of 1 per 20,000 live births and is considered an orphan disease. It has multiple forms of inheritance but is most frequently autosomal dominant. It is caused by a mutation in genes encoding alpha 1 and alpha 2 chains of type 1 collagen or by a mutation in proteins involving posttranslational modification of type 1 collagen fibers. (2)(4) The original classification by Sillance in 1979 proposed 4 OI types that were based on clinical and radiologic findings only. In 1981, Barsh and Byers (5) were the first to find reduced secretion of structurally normal type 1 procollagen in a patient with OI. By the end of that decade it was understood that nonsense and missense mutations of collagen genes (*COL1A1/COL1A2*) give rise to type I and types II to IV OI, respectively. As of 2015, with recent advancements in molecular technologies, the classification has been expanded to include up to 17 types of OI and the rare disorders Bruck syndrome 1 and 2, which are a combination of OI with contractures. (2)(6)

Clinical manifestations of OI can include excess or atypical fractures, short stature, scoliosis, basilar skull deformities that can cause neurologic symptoms, blue sclerae, progressive hearing loss, dentinogenesis imperfecta, increased laxity of the ligaments and skin, wormian bones, and easy bruising. Many of these patients eventually develop significant morbidity from respiratory insufficiency.

Diagnosis

The clinical diagnosis of OI as proposed by the 2015 Nosology and Classification of Genetic Skeletal Disorders can be fairly straightforward when there is a positive family history, typical physical features, and radiologic findings as previously described. However, in milder cases, where few clinical symptoms are observed and/or the family history is unknown, making a definitive diagnosis is more difficult. The current available molecular diagnostic test of OI uses next-generation gene sequencing to target gene panels and, therefore, is more cost-efficient with a faster turnaround time than traditional Sanger sequencing. (7)

Management

Current treatment for OI depends on the severity of disease and starts with establishing a medical home. Current primary care recommendations for all children with OI include routine and frequent screening for hearing, vision, and scoliosis; providing yearly influenza vaccination and the 23-valent polysaccharide pneumococcal vaccines in addition to routine immunizations; and coordinating referrals to subspecialists (genetics, endocrinology, pulmonology, and orthopedics), physical therapy, and occupational therapy to assist in providing comprehensive physiotherapy. The primary goal of the general pediatrician is to work closely with a multidisciplinary team to manage this complex condition and prevent its complications. (8)

Children with mild type I OI who have normal physical activity can manage any acute fractures with orthopedic surgery and rehabilitation services. Children with moderate-to-severe OI who experience long bone deformities, scoliosis, and reduced mobility may benefit from more aggressive interventions, including bone antiresorptive therapy with the use of intravenous bisphosphonates. (6) Some studies have shown that these medications increase bone mass density, decrease fractures, and improve the functional status of patients overall. However, due to expense, adverse effects (hypocalcemia, fever, vomiting), and a lack of significantly powered clinical trials, the bisphosphonates are usually reserved for moderate-to-severe disease at the discretion of the bone health team. (2) In addition to medication, patients can benefit from surgical correction of limb bowing over time if necessary.

Our Patient

Before discharge from the hospital, a medical home was identified for the patient and her care team was notified of her diagnosis, hospital course, and follow-up recommendations. On her first visit with her primary care physician, a rapid immunization catch-up was initiated, and the patient was referred to the pediatric endocrinology, orthopedic surgery, genetic counseling, and early intervention services for physical therapy and occupational therapy to help maximize bone health while formulating a plan for safe physical activity and ambulation as the patient progresses in her motor development. Unfortunately, she has since experienced another femur fracture before being fully integrated into the care of a multisubspecialty team, which has delayed the initiation of bisphosphonate therapy and comprehensive physiotherapy.

Lessons for the Clinician

- Not all skull fractures accompanied by other fractures in different stages of healing are child abuse.
- Clinicians should consider congenital or acquired bone disease such as osteogenesis imperfecta, rickets, or hypophosphatasia in the differential diagnosis of nonaccidental trauma, especially with a personal or family history of frequent fractures, abnormal sclerae, or atypical teeth.
- For concerning findings in the newborn nursery, subspecialist consultation before discharge to establish a diagnosis and/or careful follow-up of abnormal studies (including contacting the chosen primary care provider) are crucial to prevent delay in care and to limit complications.
- Osteogenesis imperfecta is a complex genetic condition that causes excessive fractures and requires a well-coordinated medical home using the hallmark therapies of bisphosphonates and physiotherapy to optimize growth, development, and bone health.

References for this article are at http://pedsinreview.aappublications.org/content/39/7/366.

Index of Suspicion

4

Recurrent Orange Urine and Abdominal Pain in a 13-year-old Boy

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AUTHOR DISCLOSURE Drs Newman and Kandikattu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy presents with acute kidney injury (creatinine level, 5.6 mg/dL [495 μmol/L]) and hypertension (blood pressure, 133/59 mm Hg). He notes 18 months of recurrent monthly episodes of back and abdominal pain, dark orange discoloration of urine, difficulty voiding, nausea, and anorexia. Most episodes occur the evening or morning after a day playing outside vigorously. His history includes anemia empirically treated with iron since childhood and occasional staring spells not previously investigated. Physical examination reveals an obese white boy without obvious dysmorphic features, abdominal masses, or tenderness and normal neurologic examination findings.

Evaluation reveals elevated serum (12.5 mg/dL [743.6 μmol/L]) and urine (31.9 mg/dL [1,897.6 μmol/L]) uric acid levels (fractional excretion, 10.48%) and a low hemoglobin level (9.8 g/dL [98 g/L]) with elevated mean corpuscular volume (93.9 fL), mean corpuscular hemoglobin level(31.3 pg), and reticulocytes (6.7%). Haptoglobin, iron, folate, and vitamin B_{12} levels are normal. Renal ultrasonography shows no nephrolithiasis. Serum creatine kinase, lactate dehydrogenase, myoglobin, and total porphyrin levels are normal. Urine studies were positive for myoglobin, with normal random calcium levels and calcium to creatinine ratios. The patient is managed with intravenous fluids and started on allopurinol with the concern of elevated uric acid production. Whole exome sequencing confirms the suspected diagnosis.

DISCUSSION

The patient's presentation was suspicious for recurrent exercise-induced rhabdomyolysis, likely secondary to metabolic myopathy. The presence of an elevated uric acid level was unusual, broadening the differential diagnosis to include partial hypoxanthine-guanine phosphoribosyltransferase deficiency or other defects in uric acid metabolism. Whole exome sequencing revealed a de novo substitution (p.S62N) in the *PGK1* gene associated with phosphoglycerate kinase deficiency. A red blood cell enzyme assay confirmed low levels of phosphoglycerate kinase B (<48 U/g hemoglobin; normal values, 165-239 U/g hemoglobin), with elevated levels of quantitative glucose-6-phosphate dehydrogenase (14.3 U/g hemoglobin [0.24 nkat/g hemoglobin]; normal values, 8.8–13.4 U/g hemoglobin [0.15–0.22 nkat/g hemoglobin]) and pyruvate kinase (16 U/g hemoglobin [0.27 nkat/g hemoglobin]; normal values, 6.7-14.3 U/g hemoglobin [0.11-0.24 nkat/g hemoglobin]).

Phosphoglycerate kinase 1 deficiency is a rare X-linked recessive disorder characterized by hemolytic anemia, myopathy, and neurologic dysfunction (Online Mendelian Inheritance in Man entry 311800). Phosphoglycerate kinase 1 catalyzes the conversion of 1,3-disphosphoglycerate to 3-phosphoglycerate during glycolysis. Clinical presentation includes hemolytic anemia, (1)(2) myopathies, (3) and neurologic involvement. (1)(2)(4)(5) Patients can express any combination of manifestations. Myopathic involvement can be severe, including rhabdomyolysis with subsequent renal failure (6) and several reports of recurrent, exercise-induced myoglobinuria. (1)(3) Clinician's should be aware of the variable manifestations of phosphoglycerate kinase 1 deficiency and consider this and other metabolic myopathies in patients with unexplained recurrent myoglobinuria.

Lessons for the Clinician

- Metabolic myopathies should be considered in patients with recurrent myoglobinuria.
- Whole exome sequencing can be performed when there is a high index of suspicion, given the number of genes and mutations that can result in metabolic myopathy.

References for this article are at http://pedsinreview.aappublications.org/content/39/7/370.

in Brief

Safety: Texting while Driving

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AUTHOR DISCLOSURE Drs Burrell and Mistry have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

The number of wireless devices in the United States surpasses the US child and adult population combined: close to 396 million wireless devices are used, and most (262 million) are smartphones. As smartphones have become more ubiquitous, text messaging has grown in acceptance. More than 70% of wireless mobile device users text at least once per day. However, among American teens, the prevalence is significantly higher, with 1 in 3 sending greater than 100 text messages per day. Moreover, recent trends indicate text messaging to be the primary method of communication between teens, thereby making texting while driving (TWD) a growing cause for concern.

Teen drivers are novice drivers and are already at heightened risk for motor vehicle accidents (MVAs) and motor vehicle–related deaths. On average, 6 teens die every day from MVAs in the United States, making it the leading cause of death in this age range. Novice teen drivers lack experience and ability to perform complex driving tasks, have lower proficiency in detecting and responding to hazards, and are more likely to engage in risk-taking behaviors on the road.

Teen drivers also represent the highest proportion of distracted drivers. Distractions occur when drivers move their attention from the task of driving to focusing on another activity. Distracted driving contributes to approximately 10% of all motor vehicle fatalities and 17% of all motor vehicle injuries in the United States. Among teens, TWD is a growing contributor to distracted driving, and it is especially dangerous because it involves 3 types of distractions—visual, manual, and cognitive attention.

Texting while driving has been associated with a fourfold increase in MVAs and results in longer breaking times, slower driving speeds, and an increase in speed variability and lane positioning. In addition, findings have shown that teens who TWD exhibited prolonged and frequent glances away from the road, up to 400% more time compared with when they are not texting. Glances away from the road that exceed 1.6 to 2.0 seconds are known to increase the risk of an MVA, and typing a simple message, "I'm on my way home," takes 37 seconds on average while driving.

Special consideration should be given to teen drivers with attention-deficit/hyperactivity disorder (ADHD). Teens with ADHD are at higher risk for driving impaired if TWD compared with teens who do not have ADHD. In simulation studies, texting was found to triple the risk of leaving one's own lane if the teen was diagnosed as having ADHD compared with doubling the risk for non-ADHD teens.

Also, TWD is associated with other risky driving behaviors. For example, teens who engage in TWD have a fivefold increase in odds of also driving while drinking alcohol and are more likely to be a car passenger with a driver who has been drinking alcohol. Teens engaging in TWD also had greater odds of wearing a seatbelt irregularly.

Texting while Driving and Other Risky Motor Vehicle Behaviors among US High School Students. Olsen EO, Shults RA, Eaton DK. *Pediatrics*. 2013;131(6):e1708–e1715

A Meta-analysis of the Effects of Texting on Driving. Caird JK, Johnston KA, Willness CR, Asbridge M, Steel P. *Accid Anal Prev*. 2014;71;311–318

Adolescent Cellphone Use While Driving: An Overview of the Literature and Promising Future Directions for Prevention. Delgado MK, Wanner KJ, McDonald C. *Media Commun*. 2016;4(3):79–89

Preventing Texting while Driving: A Statement of the American College of Preventive Medicine. Sherin KM, Lowe AL, Harvey BJ, et al. *Am J Prev Med*. 2014;47(5):681–688

Nearly half of teens report TWD, and among those reporting TWD, nearly 1 in 4 teens engaged in TWD every day. Although teens often recognize TWD as dangerous, they fear being disconnected from their peers and feel pressure to rapidly respond. Other factors used in decision making regarding whether to TWD include driving conditions, purpose of text, and the relationship with the person texting. Furthermore, parental driving behavior influences teen driving behavior. Approximately 3 of 4 teens have seen their parents engaging in TWD and report it to be common among peers. Thus, parent modeling and normative beliefs of TWD play an important role in determining teen behavior.

State legislation prevention strategies have been developed to aid in reducing the rate of TWD. Since the implementation of state laws in 2007, TWD was lowest in states with universal texting bans. Likewise, in states that universally banned TWD and made it a primary offense, there was an 8% decrease in fatalities. However, there was a loss of effect after 3 months of implementation; this trend toward low effectiveness is thought to be the result of drivers not believing the law was enforced.

To improve awareness, mass media campaigns, such as the National Safety Council's implementation of "Distracted Driving Awareness Month" in April and the Texas Department of Transportation's spearheading of "Teens in the Driver's Seat," have focused on messaging to encourage teens to remove distractions while driving. Also, phone carrier AT&T and the Governors Highway Safety Association partnered to support the media campaign "It Can Wait." Despite limited literature on the effectiveness of such efforts, these strategies can serve an important role in shifting cultural norms on TWD and begin a discourse on safe driving measures. Studies investigating teen perception of TWD have shown that messages focused on the benefits of abstaining from TWD are more effective than strategies highlighting the dangers of TWD.

Additional strategies such as smartphone apps have been marketed as tools for reducing TWD. These apps include "Live2Text" that blocks incoming texts and calls while driving and sends a message that the driver cannot respond now. Other apps use the global positioning system (GPS) to eliminate the phone's ability to text if the car is moving at a speed of approximately 10 mph or greater. Currently, there is a paucity of research examining the effects of smartphone apps on TWD.

Community partnerships between hospitals and schools in producing peer-led educational programs to reduce TWD in teens have demonstrated a significant decline in TWD with short-term follow-up. Although labor-intensive, interventions capitalizing on personal relationships with trusted authorities in teens' lives to provide accurate advice on TWD, coupled with reinforcement of safe driving messages have shown promise for reducing TWD compared with driver-centered approaches.

The pediatrician, an often trusted authority for teens, can also play a vital role in preventing TWD. The American Academy of Pediatrics recommends that pediatricians discourage distractions while driving, including the use of a mobile device. Although pediatricians are more likely to counsel teens and their families on at least 1 driver safety topic compared with other specialties, TWD is not discussed as frequently as seatbelt and alcohol use. In fact, less than one-quarter of pediatricians report always or almost always addressing TWD with teens and/or their parents.

Pediatricians have an opportunity to engage parents in a discussion on modeling appropriate behavior concerning TWD. Pediatricians can improve parental awareness of high-risk situations for teen drivers and empower parents to develop a parent-teen driving agreement that delineates parental expectations and limits on TWD. Such agreements, as proposed by the Centers for Disease Control and Prevention (CDC), encourage bidirectional communication and active participation from parents and teens in establishing safe practices for teen drivers. Anticipatory guidance that promotes self-efficacy for teens can also aid in reducing TWD in this age group. Combining multiple strategies for a comprehensive multipronged approach to prevent TWD among teens may lead to the best outcomes in changing behavior and improving the safety of teen drivers.

Note. The views expressed in this article are those of the authors, and no official endorsement by the Agency for Healthcare Research and Quality or the Department of Health and Human Services is intended or should be inferred.

COMMENT: This *In Brief* addresses a critically important issue that has emerged over the past few years with the tremendous increase in use of social media. The scope of the problem of TWD may be underestimated because many of the studies have obtained the data by reliance on adolescent self-report. Although more research needs to be conducted to evaluate effectiveness of interventions, it seems that a multipronged preventive approach may be beneficial. One strategy may include asking the question "Do you text and drive?" at all physician visits, including health maintenance, acute care, and emergency department visits. This would help highlight and perhaps reinforce in the consciousness of adolescents the importance of this issue. Parents serve as role models, and because adolescents will often emulate their parents' behaviors, addressing this issue to parents is also needed. Although studies show that adolescents recognize the dangers with TWD, they still report participating in the behavior. As with other injury prevention strategies, it seems that a focus on why abstaining from TWD is beneficial is a more powerful approach than the focus on harm. For some adolescents, compulsive texting may be a behavioral addiction and may need to be addressed. Other innovative strategies that need further evaluation include peer to peer education, school-based interventions, messages on social media, and capabilities to directly observe behaviors while driving.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

CME Quiz Clarification

An astute reader noted a need for clarification in the CME quiz for the May 2017 review "Screening for Poverty and Poverty-Related Social Determinants of Health" (Berman RS, Patel MR, Belamarich PF, Gross RS. *Pediatric Rev.* 2018; 39(5):235-246, DOI: 10.1542/pir.2017-0123). The child featured in the question 5 stem has been changed from a 1-year-old-boy to a 7-year-old boy to more closely coincide with the answer options presented. The online version of the quiz has been updated, and a clarification notice has been posted with the online version of the article. The journal appreciates the clarification.

CME Quiz Correction

An error appeared in the print version of the CME quiz for the June 2018 review "*Staphylococcus aureus*" (Ondusko DS, Nolt D. *Pediatr Rev.* 2018;39(6):287-298, DOI: 10.1542/pir.2017-0224). In question 5, the platelet count should read "85 x $10^3 \mu$L (85 x 10^9/L) …" The online version of the quiz is correct, and a correction notice has been posted with the online version of the article. The journal regrets the error.

SGA and VLBW Infants: Outcomes and Care

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AUTHOR DISCLOSURE Drs Jackson and Harrington have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Given the recent advances in medical care, babies are surviving at smaller birthweights. Categories have grown from normal birthweight (>2,500 g) to include low (<2,500 g), very low (VLBW, <1,500 g), extremely low (<1,000 g), and micro-premie (<750 g) birthweights. In addition, the categories of small and large for gestational age remain in place. Intrauterine growth retardation (IUGR) pertains to the fetal environment that can be affected by fetal, placental, or maternal factors, which is different than small for gestational age (SGA), which only defines a baby born at a weight more than 2 SD below the 50th percentile for their gestational age (ie, <10th percentile). Herein we discuss the complications, care, and outcomes for SGA (most likely caused by IUGR) and VLBW infants.

COMPLICATIONS/MANAGEMENT

The 2 categories share many of the same complications and concerns given that both infants are small but to varying degrees. However, infants who are VLBW are usually due to prematurity, whereas infants who are SGA may result from maternal complications due to pregnancy-induced or chronic hypertension, diabetes, collagen vascular disease of which systemic lupus is most prominent, asthma, chronic renal disease, receipt of anticonvulsant drugs, or use of substances such as tobacco, marijuana, and other drugs of abuse. Obviously, the complications worsen with smaller size and earlier gestational age at birth. Respiratory problems are a major concern. Asphyxia and/or meconium aspiration at birth requires immediate resuscitation and possible intubation. Decreased surfactant production in the premature infant can lead to respiratory distress syndrome and requires administration of endotracheal surfactant. Infants can have apnea of prematurity, requiring caffeine. Infants should be on continuous pulse oximetry and be given supplemental oxygen to maintain oxygen saturations of 85% to 92%.

Temperature maintenance is difficult for small infants because they have a large surface area to body weight ratio and low brown fat stores. They have difficulty in both conserving and creating body heat. These infants should be rapidly and copiously dried at birth to prevent loss of heat from evaporation. They should then be placed in warmed blankets or plastic wrap (depending on weight) to avoid loss of heat from radiation and convection. To maintain temperature, infants should be swaddled and placed in a radiant heater or an incubator (again, depending on weight).

Along with low temperatures, these infants are also at risk for low blood sugar levels. Glucose levels should be measured immediately after birth and with frequency dependent on stability. Goal glucose levels are greater than 45 mg/dL (>2.5 mmol/L). Feedings or intravenous fluids (depending on gestational age and developmental ability) should be started as soon as possible. For symptomatic

Prognosis of Very Low-Birthweight Babies. Campbell D. *Pediatr Rev.* 1997;18(3):99–100

Delayed Introduction of Progressive Enteral Feeds to Prevent Necrotizing Enterocolitis in Very Low Birth Weight Infants. Morgan J, Young L, McGuire W. *Cochrane Database Syst Rev.* 2014;12:CD001970

Slow Advancement of Enteral Feed Volumes to Prevent Necrotizing Enterocolitis in Very Low Birth Weight Infants. Morgan J, Young L, McGuire W. *Cochrane Database Syst Rev.* 2015;10:CD001241

Babies Who Are Small for Gestational Age. Russell BK. *Pediatr Rev.* 1995;16(9):354

The Small-for-Gestational Age Infant. Thureen PJ, Anderson MS, Hay WW. *NeoReviews.* 2001;2(6):e138–e149 hypoglycemia (ie, coma, seizure) or severe hypoglycemia (glucose level <20 mg/dL [<1.1 mmol/L] lasting for >30 minutes), a 10% dextrose in water bolus should be given at 2 mL/kg then run continuously at 4 to 8 mg/min per kilogram.

Fluids and gastrointestinal issues are also of concern. The VLBW infants are specifically sensitive to fluid imbalances given their high levels of insensible water losses and underdeveloped kidneys. They can have too much or too little fluid, high or low sodium levels, high potassium levels, high magnesium levels (often from the patient's mother receiving it during labor), or low calcium levels. They struggle with managing free water, reabsorbing bicarbonate, excreting potassium, and concentrating urine. Hyperbilirubinemia can also be seen. The indirect form can be seen in both SGA and VLBW infants as a sequela of prematurity, whereas the direct form can sometimes be seen in the VLBW infants who received total parenteral nutrition (TPN).

When and how quickly to feed VLBW infants is a topic of debate. One must balance the need to provide nutrition and energy to grow with the risk of necrotizing enterocolitis (NEC) in immature guts. A literature review in 2014 showed no evidence that the risk of developing NEC was decreased by waiting more than 4 days to start enteral feeds. Another review in 2015 showed that advancing feeds more quickly (30–40 mL/kg per day vs 15–24 mL/kg per day) also did not raise the probability of developing NEC. In fact, it showed that the slower rate of increase (and the consequent delay in achieving full feeds), led to a higher risk of developing a serious infection. In addition, when possible and available, maternal or banked human milk can provide added benefit to preventing NEC. All infants who cannot feed by mouth should be started on fluids at a rate of 60 to 80 mL/kg per day without sodium or potassium. Fluid amounts taken in and excreted out and electrolyte levels should be monitored closely. If infants are very small and/or are on significant life support, TPN may need to be initiated to bridge the gap and should be without lipids for the first 3 to 5 days.

Hypotension is commonly seen in VLBW infants. Umbilical lines should be placed to give more accurate recordings of blood pressures as well as to allow for blood collection until a more permanent line can be placed. Management includes starting dopamine at 5 μg/kg per minute and adjusting as needed. Fluid boluses should not be given reflexively unless there are obvious signs of hypovolemia as infants are already at risk for fluid overload and hyponatremia.

Mothers with SGA infants are specifically at risk for polycythemia, which can lead to hyperviscosity of the blood, defined as a venous hematocrit value greater than 60%. Infants do not usually have symptoms, but when they do, it is more likely to be seen in males. Consequences include hypoglycemia, hypoxia, and an increased risk of NEC. Management should include glucose and oxygen supplementation as needed and possibly partial volume blood exchange.

OUTCOMES

Survival for these infants depends on many factors. Broken down by birthweight alone, 1-year survival is 74% for infants weighing 500 to 750 g, 82% for 751 to 1,000 g, 92% for 1,001 to 1,250 g, and 95% for 1,251 to 1,500 g based on the National Vitals Statistical Summary in 2016.

Both VLBW and SGA infants face increased rates of readmission to the hospital, especially for respiratory tract infections. Final growth is difficult to predict in these infants because the causes of their initial low weights are various and often multifactorial. Neurodevelopmental difficulties are commonly seen in these infants (5–10 times more in SGA versus appropriate-for-gestational age), and cerebral palsy is common in the VLBW infants and seen more often with lower birthweights.

Infants with VLBW are at risk for long-term ophthalmologic and hearing deficits. Retinopathy of prematurity, strabismus, and refractive errors are not uncommon. Oxygen saturations should be kept at 85% to 92% to prevent high arterial oxygen tensions and decrease the risk of retinopathy of prematurity. Ophthalmologic examinations should begin at 1 month of age if less than 32 weeks' gestational age. Hearing deficits can be attributed to prematurity, hyperbilirubinemia, meningitis, and exposure to ototoxic drugs. Approximately 2% to 3% of VLBW infants may be deaf and will require further interventions. All infants should receive a hearing test in the nursery and later with their pediatrician, but it is vitally important for pediatric health care providers and the parents of the small, premature infants to ensure follow-up on any abnormalities.

COMMENT: Although medical advances have improved mortality rates and prognosis, the limit of viability for premature infants still remains at approximately 24 weeks, which was the same threshold when I was an intern several decades ago. Critical research continues to be conducted to assist in improving treatment and outcomes, but research in infants who are extremely premature and extremely low birthweight will require multisite neonatology research networks because patient numbers at individual institutions are too limited. This *In Brief* also reinforces the critical need for continued preventive research to prevent prematurity and preventive strategies for mothers who have some of the diagnoses that lead to SGA infants.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

ANSWER KEY FOR JULY 2018 PEDIATRICS IN REVIEW

Genetic Counseling in Pediatrics: 1. A; 2. B; 3. A; 4. C; 5. B.
Disorders of the Umbilical Cord: 1. B; 2. C; 3. C; 4. D; 5. D.
Vomiting in Children: 1. E; 2. C; 3. B; 4. C; 5. C.

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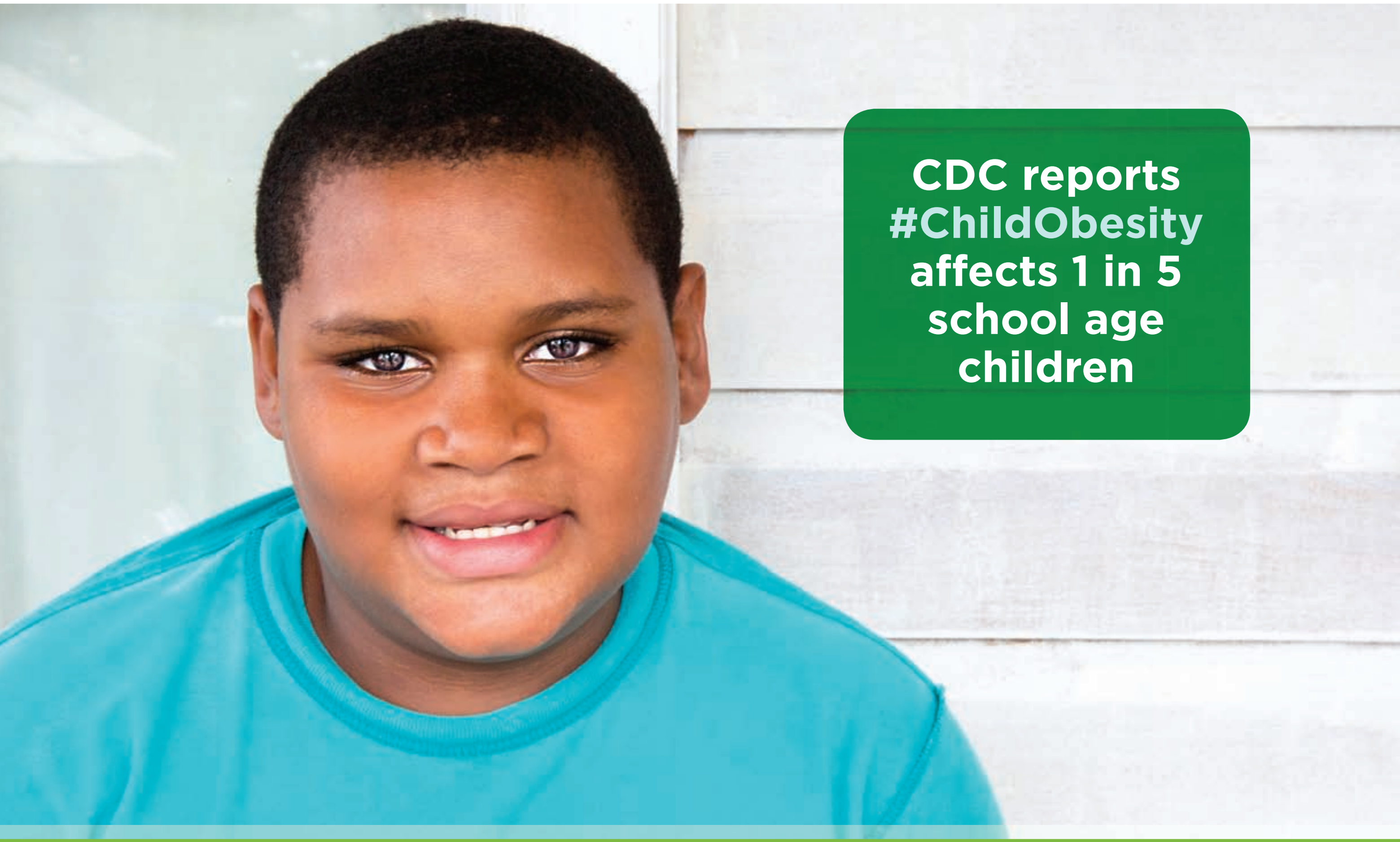

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Visual Diagnosis

A Ring of Long, Dark, Coarse Hair on the Scalp of a 5-month-old Girl

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†Toronto Dermatology Centre, Toronto, Ontario, Canada

PRESENTATION

A 5-month-old girl presents with an abnormal hair pattern on the scalp that was first noted at birth. The infant is born at term to a gravida 2, para 1 28-year-old mother after an uncomplicated pregnancy and a normal vaginal delivery. There is no history of maternal use of medication during pregnancy. The infant's birthweight is 3,200 g, length is 20.2 in (51.2 cm), and head circumference is 13.9 in (35.4 cm), each approximately at the 50th percentile. The neonatal course is uneventful. Her developmental milestones are normal. The parents are healthy and nonconsanguineous. There is no family history of craniospinal disorder or other similar disorders.

On examination, the infant is alert. There is a ring of high-density, long, dark, and thick terminal hair surrounding a patch of alopecia (Fig 1). The lesion is smooth, macular, and in the midline. The anterior fontanelle measures 0.5 × 1 cm and is not bulging. The posterior fontanelle is closed. The neurologic examination findings are normal. There is no palpable skull bone defect below the lesion. The results of the rest of the physical examination are normal.

DIAGNOSIS

This patient has a hair collar sign. Identification is based on the physical findings of a ring of long, dark, coarse hair on the scalp usually surrounding a congenital

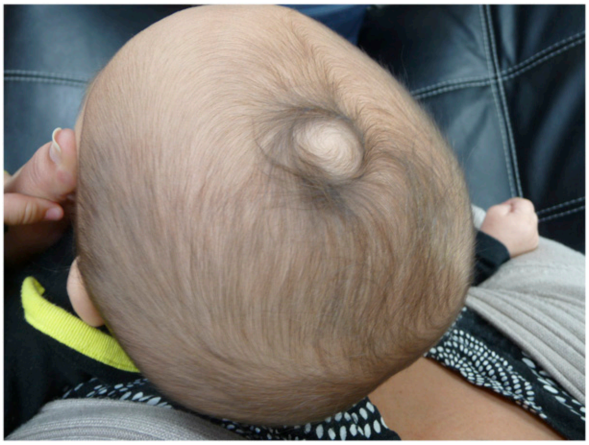

Figure 1. Hair collar sign: a ring of high-density, long, dark, and thick hair surrounding an alopecic patch.

AUTHOR DISCLOSURE Dr Leung has disclosed no financial relationships relevant to this article. Dr Barankin has disclosed that he attends advisory boards and gives continuing medical education talks for AbbVie, Actelion, Amgen, Celgene, Galderma, Janssen, La Roche Posay, Leo Pharma, Novartis, Pierre Fabre, SkinCeuticals, Tribute Pharma, and Valeant and that he receives support for clinical trials from Allergan, Amgen, AbbVie, Eli Lilly, Galderma, Janssen, and Leo Pharma. The commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

scalp lesion, such as an area of alopecia (as is illustrated in the present case), a nodule, or nevus sebaceous of Jadassohn.

DISCUSSION

The term *hair collar sign* was coined in 1989 by Commens et al, (1) who reported 2 children with cutaneous heterotopic brain tissue surrounded by a collar of long, coarse hair. The authors pointed out that the hair collar sign may suggest an underlying neuroectodermal defect. The abnormal hair pattern is most often located at the vertex, followed by the parietal regions. (2)(3) The ring of terminal hairs is typically seen surrounding a midline developmental defect such as an alopecic lesion.

The exact pathogenesis of hair collar is not known. It has been postulated that the condition results from an abnormal expression of adhesion of neural cell molecules and an increase in local production of neurotrophic growth factors. (1)(2)(3) The darker and thicker hair could also be explained by the displacement of hair follicles at the border of the lesion. (4) Histologically, there is an increased number of hypertrophied hair follicles in the hair collar. Heterotopic neural tissue may also be seen in the hair collar.

Data on the incidence and prevalence of hair collar sign are lacking. There is a slight female predominance. (5) The lesion is congenital; the average age at presentation is 4.5 months. (5) The size of the typically solitary lesion at presentation is usually less than 2 cm. (5)

The hair collar sign can be seen in some scalp malformations. More importantly, it can be a cutaneous marker for cranial neuroectodermal defects. (4)(5)(6) The hair collar sign has been shown to be associated with aplasia cutis congenita, nevus sebaceous, dermal melanocytosis, dermoid cyst, heterotopic meningeal nodule, meningeal heterotopia, meningothelial hamartoma, primary cutaneous paraganglioma, cranial meningocele, encephalocele, oculoectodermal syndrome, arteriovenous fistula, and sinus pericranii. (1)(2)(3)(4)(5)(6) Approximately one-third of cases are associated with an underlying skull defect. (5) Another one-third of cases are associated with an underlying neurocranial anomaly, notably meningeal heterotopia and atretic meningocele. (5) An isolated hair collar sign, however, is not predictive of any specific underlying anomaly.

Skull radiography should be performed to rule out an underlying bony defect. Transfontanellar ultrasonography (if the anterior fontanelle is still open), cranial computed tomography, or magnetic resonance imaging should be performed to evaluate for intracranial involvement.

Treatment depends on the underlying cause. Hair collar sign does not require any treatment. The underlying cause, however, should be treated, if possible. A neurosurgical consult would be in order if an intracranial communication is found. The prognosis depends on the underlying cause. In general, the prognosis is worse if the hair collar is associated with a true encephalocele and less so with an atretic encephalocele, especially if the lesion is in the parietal area. (2)

PATIENT COURSE

Radiography of the skull and transfontanellar ultrasonography were performed, and the results were found to be normal. The parents were reassured accordingly. The lesion was unchanged at 6- and 12-month follow-up. The child was healthy and thriving. There were no neurologic deficits.

Summary

- The hair collar sign refers to a ring of long, dark, coarse hair on the scalp, usually surrounding a congenital scalp lesion.
- The hair collar sign can be seen in some scalp malformations such aplasia cutis congenita and nevus sebaceous.
- The hair collar sign can be a cutaneous marker for cranial neuroectodermal defects. Approximately one-third of cases are associated with an underlying skull defect.
- One-third of cases are associated with an underlying neurocranial anomaly. A skull radiograph should be performed to rule out an underlying bony defect.
- Transfontanellar ultrasonography (if the anterior fontanelle is still open), cranial computed tomography, or magnetic resonance imaging should be performed to evaluate for intracranial involvement.

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Group A *Streptococcus*

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Common Substances of Abuse

ONLINE

Visual Diagnosis: A 7-year-old Boy with Dyspnea and an Unusual Chest Radiograph

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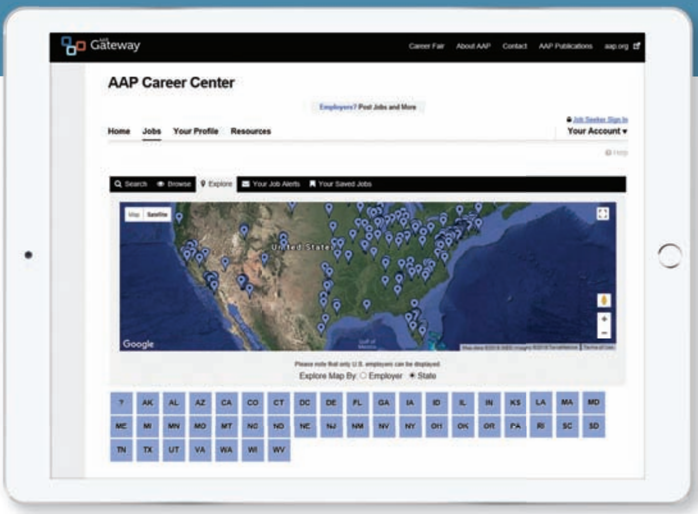

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- Neal LeLeiko, MD, PHD, disclosed he owns stocks/bonds in Celgene Corp. and serves as a paid consultant to AbbVie Inc. as a member of the data monitoring board of a new drug potentially of use in irritable bowel syndrome.
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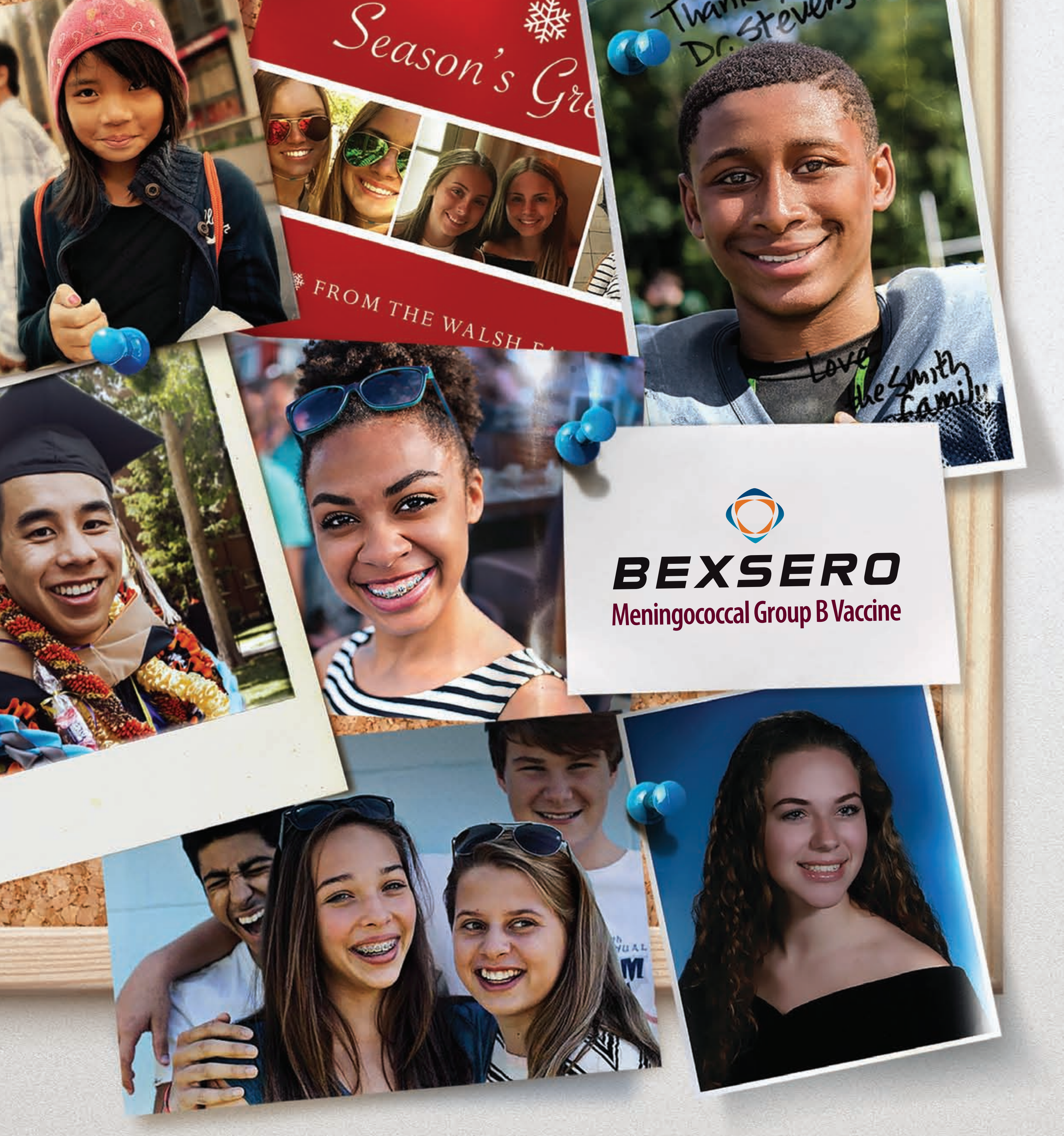

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Indication for BEXSERO

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

- BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO
- Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals
- Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope
- The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%)
- Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains
- Some individuals with altered immunocompetence may have reduced immune responses to BEXSERO
- Vaccination with BEXSERO may not result in protection in all vaccine recipients

Please see accompanying brief summary of full Prescribing Information for BEXSERO.

References: 1. Prescribing Information for BEXSERO. **2.** Prescribing Information for TRUMENBA..

BRIEF SUMMARY

BEXSERO (Meningococcal Group B Vaccine)
Suspension for intramuscular injection

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. *[see Description (11) of full prescribing information].*

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of Vaccine Effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1) of full prescribing information].*

5.5 Altered Immunocompetence

Some Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

Complement Deficiency

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N. meningitidis* serogroup B even if they develop antibodies following vaccination with BEXSERO. *[See Clinical Pharmacology (12.1).]*

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In 4 clinical trials, 3058 individuals aged 10 through 25 years of age received at least one dose of BEXSERO, 1436 participants received only BEXSERO, 2089 received only placebo or a control vaccine, and 1622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in US and Poland, 120 participants aged 10 through 25 years of age received at least one dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49% and 60% were White; 34% were Hispanic, 4% were Black,<1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) aged 11 through 17 years of age received at least 1 dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (UK), 974 university students aged 18 through 24 years of age received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1 dose of MENVEO followed by 1 dose of placebo containing aluminum hydroxide (n=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (n=947). Across groups, median age was 20 years, males comprised 46%, and 88% were White, 5% were Asian, 2% were Black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants aged 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were White, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, US/Poland, Canada/Australia, and in a subset of participants in the UK study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the US/Poland study, reports of unsolicited adverse events were collected up to one month after the second vaccination.

Reports of all serious adverse events, medically attended adverse events and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), UK (12 months), US/Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants 10 through 25 years of age following each dose of BEXSERO administered 2 months apart or control in the US/Polish study[1] are presented in Table 1 and Table 2.

Table 1: Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Local Solicited Adverse Reactions[a] within 7 Days after BEXSERO or Control, by Dose

Local Adverse Reaction		Dose 1 BEXSERO n = 110-114	Dose 1 Placebo (Saline) n = 94-96	Dose 2[b] BEXSERO n = 107-109	Dose 2[b] MENVEO n = 90-92
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	>50-100 mm	1	1	2	4
	>100 mm	0	0	0	2

Clinicaltrials.gov Identifier NCT01272180.

[a] Erythema and induration: Any (≥1 mm). Pain: Mild (transient with no limitation in normal daily activity); Moderate (some limitation in normal daily activity); Severe (unable to perform normal daily activity).

[b] Administered 2 months after Dose 1.

Table 2. Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Systemic Adverse Reactions[a] within 7 Days after BEXSERO or Control, by Dose

Systemic Adverse Reaction		Dose 1 BEXSERO n = 110-114	Dose 1 Placebo (Saline) n = 94-96	Dose 2[b] BEXSERO n = 107-109	Dose 2[b] MENVEO n = 90-92
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

(continued on next page)

Table 2. Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Systemic Adverse Reactions[a] within 7 Days after BEXSERO or Control, by Dose *(cont'd)*

Clinicaltrials.gov Identifier NCT01272180.

[a] Systemic reactions: Mild (transient with no limitation in normal daily activity); Moderate (some limitation in normal daily activity); Severe (unable to perform normal daily activity).

[b] Administered 2 months after Dose 1.

Solicited adverse reaction rates were similar among participants 11 through 24 years of age who received BEXSERO in the other three clinical studies,[2,3,4] except for severe myalgia which was reported by 3-7% of subjects. Severe pain was reported by 8% of university students in the UK[3].

Non-serious Adverse Events

In the 3 controlled studies[1,2,3] (BEXSERO n=2221, control n=2204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) receiving BEXSERO and 197 (9%) control recipients. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in participants receiving BEXSERO than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants aged 10 through 25 years of age who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO n=2716, Control n=2078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) participants receiving BEXSERO and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at 2 universities in the US, BEXSERO was administered as a 2-dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals aged 16 through 65 years of age who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one event considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

Adverse event reports received for BEXSERO marketed outside the US are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency, or to establish a causal relationship to vaccination. This list includes serious events or events which have suspected causal association to BEXSERO.

General Disorders and Administration Site Conditions:	Injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site, and injection site nodule which may persist for more than 1 month).
Immune System Disorders:	Allergic reactions (including anaphylactic reactions), rash, eye swelling.
Nervous System Disorders:	Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility in females or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Pregnancy Registry for BEXSERO

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to BEXSERO during pregnancy. Women who receive BEXSERO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years of age.

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17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

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American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Group A *Streptococcus*

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Education Gaps

1. Clinical prediction rules for group A *Streptococcus* pharyngitis are unreliable in children, and unless viral etiology is strongly suspected, throat swab with a rapid antigen detection test should be performed.
2. Avoid "proof of cure" cultures when treating pharyngitis.
3. Clindamycin is important in invasive group A *Streptococcus* infection for toxin mediation but should not be used alone secondary to possible resistance.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology, transmission, and major virulence factors of group A *Streptococcus* (GAS) infections.
2. Plan the appropriate diagnostic evaluation of suspected GAS infection.
3. Recognize the clinical features of, and major complications associated with, invasive and noninvasive GAS infections.
4. Plan appropriate management for a patient with a GAS infection.

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ABBREVIATIONS

ANF	acute necrotizing fasciitis
ARF	acute rheumatic fever
GAS	group A *Streptococcus*
IVIG	intravenous immunoglobulin
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *S aureus*
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PSGN	poststreptococcal glomerulonephritis
STSS	streptococcal toxic shock syndrome

INTRODUCTION

In 1933, Rebecca Lancefield changed our understanding of β-hemolytic streptococci by developing a system of serologic classification based on the carbohydrate composition of cell wall antigens. Of these organisms, the most significant in human pathogenicity is group A *Streptococcus* (GAS), otherwise known as *Streptococcus pyogenes*. (1) GAS is responsible for an impressively wide variety of clinical manifestations, from noninvasive infections, such as pharyngitis, scarlet fever, erysipelas, and cellulitis, to invasive disease, including sepsis, streptococcal toxic shock syndrome (STSS), and necrotizing fasciitis (Table 1). It has also been linked to multiple nonsuppurative complications including acute rheumatic fever (ARF), poststreptococcal glomerulonephritis (PSGN), and the controversial pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Globally, an estimated 18 million people are suffering from a serious GAS-related illness, with about 1.78 million new cases annually. Hundreds of millions of people develop less serious GAS infection every year, placing a massive burden on healthcare systems. The complications of GAS infections disproportionately affect those in low- and middle-income countries. Transmission of GAS is via droplets from those with pharyngeal infection or colonization, direct contact, contaminated fomites, or foodborne contamination. (2)(3)

The virulence and range of infection and complications of GAS can be attributed to certain characteristics that this gram-positive bacterium possesses, including cellular constituents, extracellular products, and unique autoimmune responses it can produce. Important virulence factors include a hyaluronic acid capsule, which protects GAS from phagocytosis, and the M protein, a surface protein that is used to define serotypes of GAS. The M protein also contributes to virulence in many ways, including inhibition of opsonization and phagocytosis, as well as facilitating tissue invasion. Extracellular products are numerous and play many different roles, and include the streptococcal pyrogenic exotoxins. Toxins play a particularly important role in invasive GAS infections like STSS, in which mediation of toxin production with the protein synthesis inhibiting clindamycin is especially important. A particular group of streptococcal toxins, called *superantigens*, stimulate massive cytokine release, which is responsible for the overwhelming and rapid progression of disease that can be seen in invasive streptococcal infections. A protease toxin, SpeB, is also known to play an important role in virulence, implicated as contributing to both superficial and invasive disease. (1)(3)(4)

This review covers the major noninvasive and invasive GAS infections and complications in children, and will touch on recent research, including vaccine development and burgeoning resistance.

TABLE 1. **Various Infection Types with Group A *Streptococcus***

TYPES OF INFECTION	
Noninvasive	Pharyngitis Otitis media Sinusitis Impetigo Erysipelas Cellulitis Vulvovaginitis Dactylitis Pneumonia without bacteremia
Invasive	Sepsis Focal infections with bacteremia Streptococcal toxic shock syndrome Necrotizing fasciitis Meningitis Peritoneal infection Septic arthritis Osteomyelitis Cardiac—endocarditis, pericarditis
Non-suppurative complications	Acute rheumatic fever Poststreptococcal glomerulonephritis Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

NONINVASIVE GAS INFECTIONS

Streptococcal Pharyngitis

Pharyngitis accounts for about 6% of all primary care physician visits, and about 40% of children older than 3 years presenting with a complaint of sore throat will test positive for GAS. (5)(6) It occurs most commonly in children 5 to 15 years of age during winter months. (1) Clinical signs and symptoms in school-age and older children include sore throat, fever, tender anterior cervical adenopathy, pharyngeal and tonsillar exudate (Fig 1), vomiting, and headache. Younger children and infants, on the other hand, may present with generalized lymphadenopathy, fever, and serous nasal discharge. (7)

If GAS pharyngitis is suspected, the diagnostic approach should begin with a rapid antigen detection test in children older than 3 years followed by throat culture in those who test negative. Children younger than 3 years of age are unlikely to manifest ARF, and thus diagnosis and treatment are less important. However, physicians may choose to test children younger than 3 years if risk factors are significant, for example, when symptoms are present and the child has a relative with GAS. (8) Culture is not necessary in those who test positive with the antigen test. (9) Multiple clinical prediction rules are available to aid in the diagnosis of GAS. The Centor criteria, for example, assign a point each to temperatures greater than 101.3°F (38.5°C), swollen and tender anterior cervical lymph nodes, tonsillar exudate, and absence of cough. These criteria were tested in studies that showed them to be effective in ruling out GAS pharyngitis in adult patients with 2 or fewer criteria. These criteria must be used with caution in children, however, because multiple studies have demonstrated the unreliability of clinically observable signs and symptoms. (5)(10)(11) Unless clinical findings strongly suggest a viral etiology (conjunctivitis, rhinitis, coryza, rash, cough), throat swab with the rapid test should be used to rule out GAS, and these clinical prediction rules should not be used in isolation.

The need to treat all cases of GAS pharyngitis in high-resource settings with low incidence of rheumatic fever is controversial. However, current recommendations in the

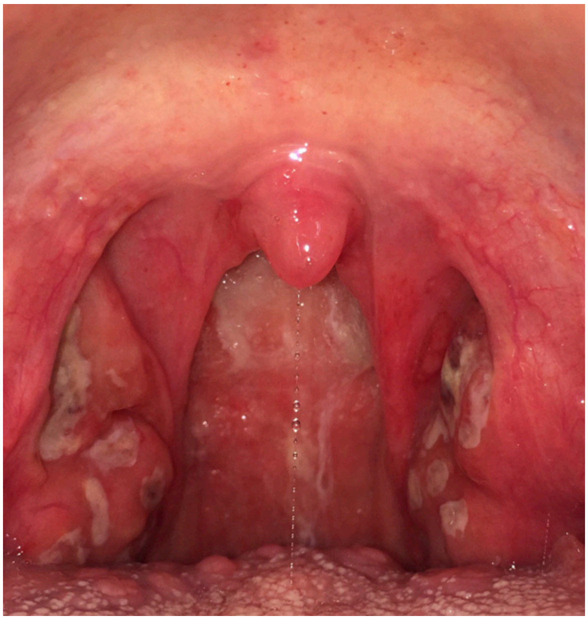

Figure 1. Tonsillar exudate and palatal petechiae in a patient with group A *Streptococcus* pharyngitis.

United States are to do so. To prevent rheumatic fever, treatment must be started within 9 days of symptom onset. Preferred oral antibiotic regimen is penicillin V or amoxicillin for 10 days. Physicians should note the benefit of once-daily dosing of amoxicillin, which may be preferred. Another option, particularly in patients who may have difficulty reliably taking oral medications, is intramuscular benzathine penicillin G. Procaine penicillin has decreased pain associated with the injection. In penicillin-allergic patients who have not had a systemic anaphylactic reaction, a first-generation cephalosporin is recommended for 10 days. Otherwise, physicians may give clarithromycin or clindamycin for 10 days, or azithromycin for 5 days. (8) Posttreatment throat cultures as proof of cure are unnecessary unless symptoms persist 2 to 7 days after completion of therapy. (12)

Scarlet Fever

Scarlet fever, or scarlatina, results from the systemic elaboration of erythrogenic GAS exotoxins, most commonly in association with GAS pharyngitis but occasionally from skin and skin structure infection. More severe manifestations are less common in areas where antibiotic treatment is readily available. The most characteristic symptom is a rash that typically begins on the upper chest or neck 1 to 2 days after the onset of GAS infection and will spread to the extremities and face. There is diffuse erythema which blanches, with a finely papular "sandpaper" texture of the skin (Fig 2), with pinpoint areas of deeper red scattered petechiae that do not blanch, and "Pastia's lines" (Fig 3), which are areas of deeper red in the skin creases. Other findings include circumoral pallor (Fig 4), strawberry tongue, and later desquamation (Fig 5). (1)(13) Treatment is focused on the underlying bacterial infection that is the nidus of toxin production and the subsequent symptoms of scarlet fever.

Acute Rheumatic Fever

ARF is an illness that involves multiple organ systems, and is the leading cardiovascular cause of death in children in low-income countries. (12) It has an onset typically 2 to 4 weeks after GAS pharyngitis; other types of GAS infection have not reliably shown an association with ARF, though there is some evidence of its occurrence. (14)(15)(16)(17) ARF is thought to be an autoimmune response via molecular mimicry. (18) The link between prior GAS infection and onset of ARF is clear, with the advent of antibiotic treatment for GAS pharyngitis leading to a sharp decline in the incidence of ARF. (19) Diagnosis is made using the Jones criteria, in which 2 major, or 1 major and 2 minor, criteria must be fulfilled along with evidence of preceding GAS infection (Table 2). Major criteria are carditis, arthritis, chorea, erythema marginatum (Fig 6), and subcutaneous nodules, while minor criteria include arthralgia, fever, elevated erythrocyte sedimentation rate, and prolonged PR interval. In 2015, the American Heart Association updated the Jones criteria, distinguishing between low- and moderate- to high-risk populations, and emphasizing the use of echocardiography in diagnosing carditis, and the inclusion of monoarthritis and polyarthralgia as major criteria in moderate- or high- risk populations. A low-risk population is one that has an ARF incidence of less than or equal to 2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of less than or equal to 1 per 1,000 population per year. (20) The incidence of primary ARF is greatest in children from 5 to 14 years of age with equal

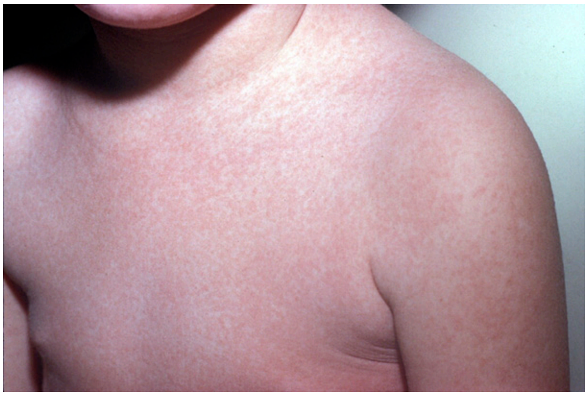

Figure 2. Diffuse erythematous sandpaper rash of scarlet fever. (74)

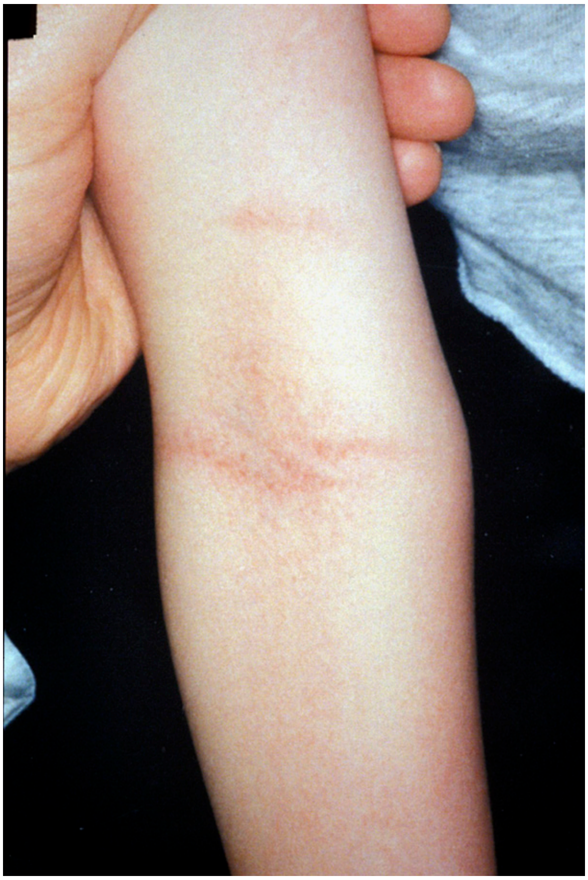

Figure 3. Pastia's lines in a patient with scarlet fever. (74)

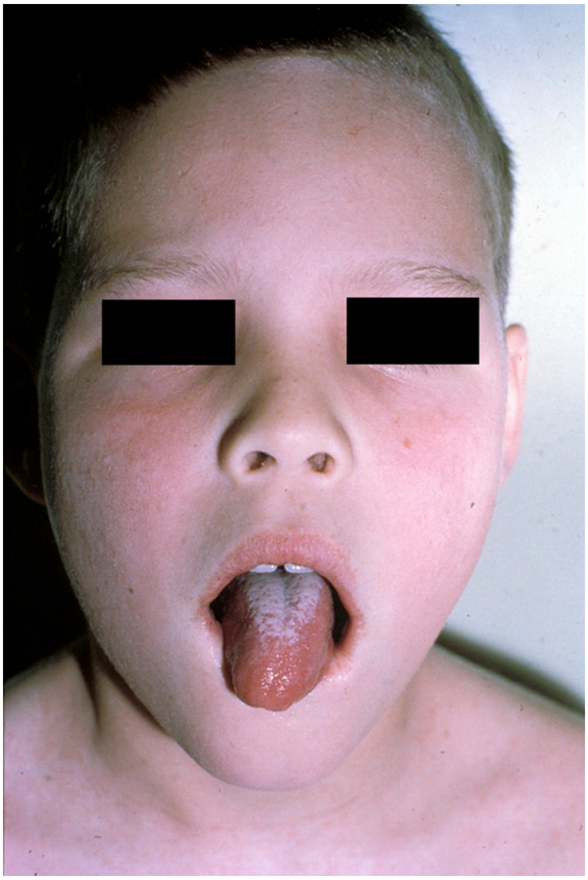

Figure 4. Circumoral pallor and strawberry tongue in a patient with scarlet fever. (74)

distribution between boys and girls, though girls have a greater incidence of associated heart disease. (18)

Management of ARF focuses on eradication of GAS along with targeted therapy toward individual manifestations. Echocardiography with Doppler should be performed on initial presentation even in the absence of auscultatory findings, and serial echocardiography should be strongly considered even if carditis is not present on initial diagnosis. (20) Carditis is treated with bed rest, fluid restriction, cardiac medications and corticosteroids, (18) though it is unclear whether corticosteroids have a true impact on long-term outcomes. (21) There has been no evidence to demonstrate the efficacy of immune-modulating medications such as intravenous immunoglobulin (IVIG). (22) Arthritis is treated with aspirin at 50 to 70 mg/kg per day tapered over several weeks, (14)(15)(16)(17)(18)(19)(20)(21)(22)(23) though there is some evidence that the naproxen is an effective alternative to control inflammation and pain, and circumvents the rare risk of Reye syndrome. (24)(25)(26) Anti-inflammatory medications should be used with caution, however, before a definitive diagnosis of ARF is made, because they can mask developing symptoms that may contribute to the diagnosis. Sydenham chorea is typically benign and self-limiting, though it can be severe and onset can be up to months after initial infection. Pharmacologic treatment may be considered in patients with severe symptoms, and may include valproic acid, carbamazepine, and short courses of steroids. (18)(27)(28)

Children with a history of ARF are at greater risk of ARF recurrence with subsequent GAS infections and should

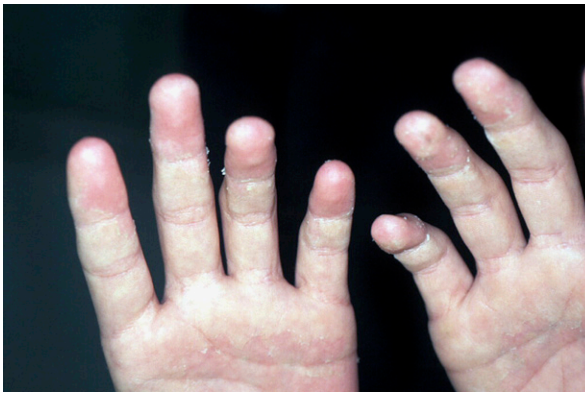

Figure 5. Desquamation of the fingertips in a patient with scarlet fever; desquamation typically occurs about 7 to 10 days after onset of illness. (74)

TABLE 2. Revised Jones Criteria for ARF from 2015 American Heart Association Statement (20)

Diagnosis of initial ARF requires 2 major criteria, or 1 major plus 2 minor criteria.
Diagnosis of recurrent ARF requires 2 major criteria, or 1 major plus 2 minor criteria, or 3 minor criteria.

	MAJOR CRITERIA	MINOR CRITERIA
Low-risk populations: ARF incidence ≤2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population per year	Carditis[a] (clinical and/or subclinical) Arthritis (polyarthritis only) Chorea Erythema marginatum Subcutaneous nodules	Polyarthralgia Fever (≥38.5°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL[b] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)
Moderate- and high-risk populations	Carditis[a] (clinical and/or subclinical) Arthritis (monoarthritis or polyarthritis) OR Polyarthralgia[c] Chorea Erythema marginatum Subcutaneous nodules	Monoarthralgia Fever (≥38°C) ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL[b] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

ARF=acute rheumatic fever; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate.
[a] *Subclinical carditis indicates echocardiographic valvulitis as defined by Gewitz et al. (20)*
[b] *CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.*
[c] *Applicable as a major criterion only after careful consideration and exclusion of other causes of arthralgia.*

begin prophylaxis as soon as ARF is diagnosed. Prophylaxis may be intramuscular benzathine penicillin G once monthly or daily oral penicillin, and for penicillin-allergic patients a macrolide is typically used. Duration of prophylaxis is 5 years since the last episode of ARF or until 21 years of age in patients who did not have carditis, whichever is later. In patients with carditis who do not have residual heart disease (no valvular disease) duration is 10 years since the last ARF episode, or until 21 years of age, whichever is later. Finally, when there are persistent manifestations of rheumatic heart disease, penicillin prophylaxis is continued until 40 years of age at a minimum, and depending on severity of disease, many clinicians choose to provide prophylaxis for life. (12)(29)

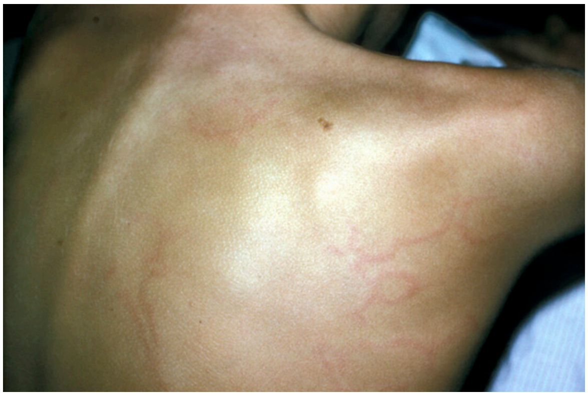

Figure 6. Erythema marginatum in a patient with acute rheumatic fever. This rash is characterized by nonpruritic, mildly raised ringlike erythema with central clearing. Although present in only a minority of cases of rheumatic fever, this finding is considered a major Jones criterion. (74)

Impetigo

Impetigo is an extremely common superficial infection of the skin described either as bullous or nonbullous. Bullous lesions are much more likely to be caused by *Staphylococcus aureus* with strains that commonly elaborate an erythrogenic toxin, whereas nonbullous impetigo may result from either GAS or *S aureus*. (30) From the 1950s through the 1970s, GAS was a more common cause of impetigo than *S aureus*, but since that time *S aureus* has become more common, accounting for more than 80% of these skin infections today. This change in etiology accounts for the decreased incidence of acute glomerulonephritis in children. Appearance of the lesion is not sufficient to identify the responsible organism; thus, if bacterial identification is desired, culture is necessary. The infection is most common in children 2 to 5 years of age, though it can occur in any age. (30) Nonbullous impetigo typically manifests in exposed areas, such as the face and limbs. It is characterized by erythematous papules, which evolve to vesicles that rapidly rupture to form characteristic "honey-colored" exudate and thick crusts (Fig 7). (31)

For more localized lesions, treatment consists of topical mupirocin or retapumulin. For more extensive or multiple lesions, oral therapy may be considered. Cephalexin, a first-generation cephalosporin, will effectively treat GAS and methicillin-susceptible *S aureus* (MSSA). Physicians should be aware of the prevalence of methicillin-resistant *S aureus* (MRSA) in their communities, and if it is suspected, consider clindamycin or trimethoprim/sulfamethoxazole for oral therapy in more severe cases. (32)(33)(34) Although impetigo is a self-limited disease, treatment can shorten the time to resolution, and thus decrease spread of the infection. Culture of the lesion to identify the offending organism can be helpful, but it is also appropriate to empirically treat most cases without performing a culture. Children with impetigo should be withheld from school or daycare for 24 hours after the initiation of treatment.

Erysipelas and Cellulitis

Impetigo is an infection of the epidermis, erysipelas is an infection of the deeper dermis, and cellulitis involves the dermis and subcutaneous tissue. These latter infections are caused primarily by GAS, though they can also result from infections with group C or G streptococci, group B streptococci, or less commonly *S aureus*. (31)(34)(35)(36) Skin lesions such as eczema, chickenpox, or lacerations can become secondarily infected with GAS (impetiginized) leading to an abscess with surrounding cellulitis termed *pyoderma*.

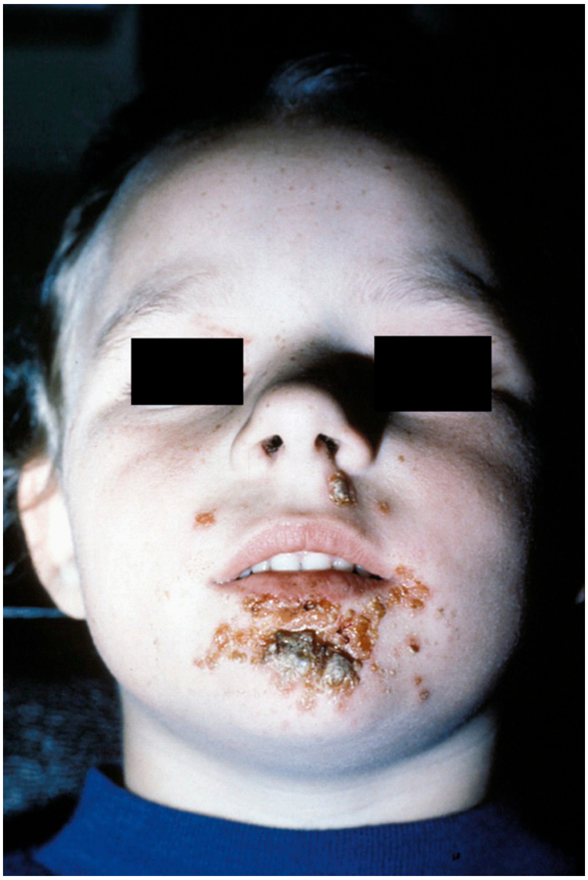

Figure 7. Impetigo with characteristic honey-colored exudate and thick crusts. (74)

Erysipelas presents as a raised, painful skin erythema with distinct borders, most often on the face or extremities (Fig 8). Frequently lymphatic involvement is seen with erythematous streaking termed *ascending lymphangitis*. Cellulitis presents as edema and erythema that is not sharply demarcated, but also with tenderness, pain, and warmth. (31) Presence of a purulent lesion is less common with GAS and should raise suspicion for *S aureus*. Treatment for erysipelas and cellulitis without purulent lesions and without systemic signs of infection should target streptococci, and many clinicians choose to include coverage against MSSA as well. For erysipelas, which is almost always caused by β-hemolytic streptococci, clinicians may treat with penicillin or amoxicillin. In cases in which it may be more difficult to distinguish between erysipelas and cellulitis and when MSSA is a consideration, for outpatient therapy a first-generation cephalosporin, such as cephalexin, or clindamycin is appropriate. Treatment for uncomplicated erysipelas and cellulitis is typically for 5 days. For more severe infections with systemic symptoms, evidence of MRSA infection elsewhere, history of penetrating trauma, or known MRSA nasal colonization, coverage against both MRSA and streptococci is recommended. Parenteral treatment should be considered for very young children; rapidly progressing erysipelas or cellulitis; large areas of involvement; involvement of the face, neck, or genitals; and children who have systemic symptoms, including fever and tachycardia. (1)(31)(34)

Vulvovaginitis and Perianal Cellulitis

Vulvovaginitis is the most common gynecologic complaint in the prepubescent girl treated by the primary care physician. Typically, a child with GAS vulvovaginitis will present with vulvar pain or itching, spotting of serous to purulent discharge on the underwear, and vulvar erythema. Perianal cellulitis with GAS presents as a sharply demarcated perianal erythema that is often painful and pruritic. Although most cultures of vulvovaginitis in prepubertal girls are polymicrobial, the most consistent agent identified is GAS. (37)(38)(39)(40) Unlike other organisms found on cultures from patients with vulvovaginitis, GAS is not considered normal vaginal bacterial flora. (41) Several reports have linked GAS vulvovaginitis to a previous pharyngeal infection or colonization with the organism, though this is not required for diagnosis. (42) Although some clinicians

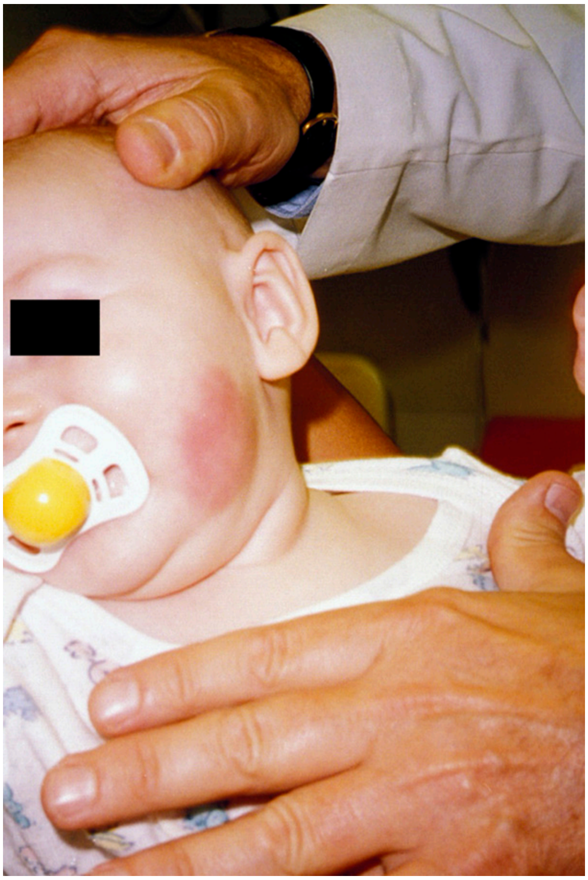

Figure 8. Erysipelas on the face of a young child. Note the distinct, raised borders of the lesion. (74)

do use rapid antigen diagnostic tests for diagnosing vulvovaginitis or perianal cellulitis, these assays have not been validated for genital infections. Etiologic diagnosis is best achieved via culture from a vaginal or perianal swab. The recommended treatment of GAS vulvovaginitis and perianal cellulitis is a 10-day course of amoxicillin; for the penicillin-allergic child, clarithromycin has been described. (41)(43)(44) If vulvovaginitis is recurrent, one should consider testing the child for pharyngeal carrier status and decolonizing. Evidence to dictate a preferred regimen is not sufficient; thus, decolonizing protocols for pharyngeal carriage may be considered (see section on "Carrier State"). Although 1 study demonstrated promising results for recurrent vulvovaginitis using topical localized treatment, this approach has not been adequately studied. (45)

Poststreptococcal Glomerulonephritis

Poststreptococcal glomerulonephritis (PSGN) is a nonsuppurative complication during and after streptococcal infection, most commonly GAS impetigo. It can range from asymptomatic to severe with subsequent renal failure, though most cases in children have few long-term complications. PSGN has an onset 2 to 4 weeks after infection in the skin and 7 to 10 days after streptococcal pharyngitis. PSGN will usually manifest as an acute nephritic syndrome, though it can also cause nephrotic syndrome, and more rarely, rapidly progressive glomerulonephritis. Presenting symptoms include hematuria, which may be microscopic or macroscopic, proteinuria, hypertension, and edema. Laboratory studies will typically be significant for evidence of a past streptococcal infection with positive ASO or anti-DNAse B antibody titers, as well as low levels of complement C3. At diagnosis of PSGN, if the GAS infection is still present, it should be treated with appropriate antibiotics. Treatment of PSGN is typically supportive in nature and depends on clinical presentation, but may include antihypertensive medications, sodium and fluid restrictions, steroid administration and, if necessary, dialysis. It is important to note that treating streptococcal infections may not prevent PSGN, but importantly, will prevent nephritogenic strains of PSGN from spreading to family members and other contacts. (46)(47)

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

Under the umbrella of obsessive compulsive and tic disorders is the subtype pediatric acute-onset neuropsychiatric syndrome, which falls within PANDAS. (48) The defining symptoms, pathophysiology, and treatment of this condition have been controversial since the diagnosis was first suggested. In general, an abrupt onset of obsessive-compulsive behaviors, tics, choreiform movements, and various behavioral manifestations characterize the disorder. (49) PANDAS must be preceded by a proven streptococcal infection with positive ASO or anti-DNAseB antibody titers and occurs typically within a few days to weeks after infection. A leading hypothesis of etiology is autoimmune, with possible basal ganglia antigens as targets. (50)

Evidence for the management of suspected PANDAS is not robust. Typically, management includes psychiatric treatments focusing on symptoms of obsessive-compulsive behaviors, tics, and behavioral manifestations. Children with active GAS pharyngitis should be treated appropriately, and prophylactic penicillin for children with frequent PANDAS exacerbations should be considered; studies for the latter have shown mixed results. (50) A recent 2015 study demonstrated a non–statistically significant improvement in tic symptoms with a 30-day course of cefdinir after a recent onset of obsessive-compulsive disorder or tics. (51) Case reports have documented improvement of PANDAS after tonsillectomy/adenoidectomy, but a large study by Murphy et al did not demonstrate a difference in children who did and did not undergo the procedure. (52) Some studies have indicated a possible benefit of plasma exchange

TABLE 3. Suggested Antibiotic Dosing for Select Group A *Streptococcus* Infections[a]

INFECTION/CONDITION	ANTIBIOTIC	DOSING	DURATION
Pharyngitis (8)(12)	Penicillin V (oral)	Children <27 kg: 250 mg 2 or 3 times daily; children ≥27 kg, adolescents, and adults: 250 mg 4 times daily or 500 mg 2 times daily	10 days
	Amoxicillin (oral)	50 mg/kg once daily	10 days
	Benzathine penicillin G (intramuscular)	<27 kg: 600,000 U; ≥27kg: 1,200,000 U	1 dose
	Cephalexin (oral)	40 mg/kg per day divided 2 times daily (max = 500 mg/dose)	10 days
	Azithromycin (oral)	12 mg/kg once daily (max = 500 mg)	5 days
	Clarithromycin (oral)	15 mg/kg per day divided 2 times daily (max = 250 mg/dose)	10 days
	Clindamycin (oral)	20 mg/kg per day divided 3 times daily (max = 300 mg/dose)	10 days
Decolonization (8)	Clindamycin (oral)	20–30 mg/kg per day divided 3 times daily (max = 300 mg/dose)	10 days
	Penicillin and rifampin (oral)	Penicillin V: 50 mg/kg per day divided 4 times daily for 10 days (max = 2,000 mg/day) and rifampin: 20 mg/kg once daily for the last 4 days of treatment (max = 600 mg/day)	10 days
	Amoxicillin-clavulanic acid (oral)	40 mg amoxicillin/kg per day divided 3 times daily (max = 2,000 mg amoxicillin/day)	10 days
	Benzathine penicillin G (intramuscular) and rifampin (oral)	Benzathine penicillin G: <27 kg: 600,000 U; ≥27 kg: 1,200,000 U and rifampin: 20 mg/kg per day divided 2 times daily (max = 600 mg/day)	1 dose of Benzathine penicillin G, and 4 days of rifampin
ARF prophylaxis (12)	Benzathine penicillin G (intramuscular)	<27 kg: 600,000 U; ≥27 kg: 1,200,000 U	1 dose every 4 weeks
	Penicillin V (oral)	250 mg 2 times daily	
	Azithromycin (oral) (erythromycin and clarithromycin can also be used)	5 mg/kg once daily	
Impetigo (34)	Mupirocin (topical)	Apply 2 times daily	5 days
	Retapumulin (topical)	Apply 2 times daily	5 days
	Cephalexin (oral)	25–50 mg/kg/day divided 3–4 times daily (max = 250 mg/dose)	7 days
	Clindamycin (oral) *(if MRSA also suspected)*	20–30 mg/kg per day divided 3 times daily (max = 300 mg/dose)	7 days
Erysipelas: Mild, nonpurulent, no systemic signs of infection, outpatient treatment[b](30)(34)(75)	Amoxicillin (oral)	40–90 mg/kg per day divided 2 or 3 times daily	5 days

Continued

TABLE 3. **(Continued)**

INFECTION/CONDITION	ANTIBIOTIC	DOSING	DURATION
Cellulitis, mild, nonpurulent, no systemic signs of infection, outpatient treatment[b](34)(75)	Cephalexin (oral)	50 mg/kg per day divided 4 times daily (max = 500 mg/dose)	5 days
	Clindamycin (oral)	25–30 mg/kg per day divided 3 times daily (max = 1,800 mg daily)	5 days
Vulvovaginitis and perianal cellulitis (42)(43)	Amoxicillin (oral)	50 mg/kg per day divided 3 times daily (max = 500 mg/dose)	10 days
	Clarithromycin (oral)	15 mg/kg divided 2 times daily (max = 1,000 mg daily)	7–10 days
Empiric therapy for STSS and streptococcal ANF (34)(29)(75)	Clindamycin (IV)	40 mg/kg per day divided 3 to 4 times daily (max = 2,700 mg daily)	
	AND		
	Meropenem (IV) (other carbapenems may also be used) OR	30–60 mg/kg per day divided 3 times daily (max = 1,000 mg/dose)	
	Piperacillin-tazobactam (IV) (other β-lactam/β-lactamase inhibitor combinations may also be used)	For children ≥9 months of age, 300 mg/kg per day piperacillin component divided 3–4 times daily (max = 16 g)	
	AND		
	Vancomycin (if Staphylococcus cannot be ruled out)	45–60 mg/kg per day divided 3–4 times daily (max = 4 g)	
Chemoprophylaxis for high-risk contacts of patients with invasive GAS (76)	Benzathine penicillin G (intramuscular) and rifampin (oral)	Benzathine penicillin G: <27 kg: 600,000 U ≥27 kg: 1,200,000 U and rifampin: 20 mg/kg per day divided 2 times daily (max = 600 mg/day)	1 dose of benzathine penicillin G and 4 days of rifampin
	Clindamycin (oral)	20 mg/kg per day divided 3 times daily (max = 300 mg/dose)	10 days
	Azithromycin (oral)	12 mg/kg per day once daily (max = 500 mg/day)	5 days

ANF=acute necrotizing fasciitis; ARF=acute rheumatic fever; GAS=group A Streptococcus; IV=intravenous; MRSA=methicillin-resistant Streptococcus aureus; *STSS=streptococcal toxic shock syndrome.*

[a] *Doses listed are not necessarily appropriate for neonates.*

[b] *For parenteral treatment or if concern for MRSA, see Stevens et al. (34)*

and IVIG in severe cases of PANDAS. (53)(54)(55) One randomized controlled trial of IVIG demonstrated no statistically significant difference between IVIG and placebo during the blinded portion of the trial, though improvement was seen during the open-label portion. (56)

INVASIVE GAS INFECTIONS

In invasive GAS infections, the organism is found in typically sterile sites such as blood, joint fluid, or cerebrospinal fluid. Based on surveillance data from the Centers for Disease Control and Prevention, between 2005 and 2012, between 1,136 and 1,607 deaths occurred per year in both adults and children in the United States secondary to invasive GAS. Among children, peak incidence occurs before 2 years of age. Invasive GAS occurs more frequently in winter and early spring. (57) Although the spectrum of invasive GAS is wide, for the purposes of this review, we will focus on 2 presentations that are important for the general pediatrician to quickly recognize: STSS and acute necrotizing fasciitis.

Streptococcal Toxic Shock Syndrome

STSS consists of infection with GAS accompanied by hypotension and evidence of multiorgan failure. STSS is usually preceded by skin or soft tissue infections with GAS, but can be seen with GAS infection at any site. In STSS, superantigen toxins trigger massive T-cell proliferation and a subsequent "cytokine storm." (58) The patient may present initially with fevers and a generalized erythroderma and then progress to develop hypotension and multiorgan failure. The pillars of treatment for STSS are aggressive management of shock and organ failure, antibiotic therapy, and consideration of IVIG administration. If soft tissue involvement is noted, including necrotizing fasciitis, emergent surgical evaluation is warranted. (29) Antibiotic treatment is dual, with a β-lactamase–resistant β-lactam, such as a penicillin/penicillinase-inhibitor combination or carbapenem, as well as clindamycin, which serves to reduce the production of superantigens by GAS. (58)(59) In addition, if staphylococcal infection cannot be ruled out, vancomycin should be added to the empiric therapy regimen. Multiple studies, including several observational studies (59)(60)(61) and 1 small, randomized control trial, (62) indicate that IVIG as an adjunctive therapy may decrease mortality in STSS. Use of IVIG is still in debate, however, and individual clinical judgment is appropriate. If IVIG is given, an acceptable dosing regimen is 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3. (29) In the United States, there is currently no recommendation to provide chemoprophylaxis to close contacts.

Acute Necrotizing Fasciitis

Type II acute necrotizing fasciitis (ANF) is an aggressive, rapidly progressing deep tissue infection caused by GAS, usually alone, but to a lesser extent in combination with *S aureus* or anaerobes. ANF accounted for 7% of all cases of invasive GAS infections in the United States between 2005 and 2012, with just less than 1% presenting with combined ANF and STSS. Mortality for all cases of ANF was 20%, though this was much lower in the pediatric population. (57) Mortality of combined ANF and STSS is much higher, with some estimates as high as 60%. (63) ANF will typically begin as an apparently innocuous lesion that may be accompanied by pain that is out of proportion with the examination findings. Infants may have profound irritability. Children may also present with fever, tachycardia, leukocytosis, elevated creatine phosphokinase, hypoalbuminemia, hypocalcemia, and evidence of coagulopathy. Within 24 to 72 hours, there is a rapid progression to more pronounced inflammation, followed by purplish discoloration of the skin, evolving into hemorrhagic or serous bullae. Over the next few days, the involved tissue, which may go as deep as muscle, will become frankly necrotic. The most important step in halting the progression of the necrosis is surgical debridement, which should not be delayed for further diagnostics if the suspicion for ANF is high. Magnetic resonance imaging may be helpful in the diagnosis but cannot rule out ANF; although gas visualized in the tissues is a classic finding in ANF, often all that is seen is localized tissue swelling. Antibiotic therapy is the same as in STSS: dual therapy with a β-lactamase–resistant β-lactam antimicrobial combined with clindamycin to mediate GAS toxin, with the addition of vancomycin until MRSA can be ruled out. (29)(63)(64) A recent large study in adults demonstrated no benefit of IVIG in mortality or length of hospital stay in patients with ANF who had undergone surgical debridement and received antibiotic therapy. (65)

CONCLUSIONS

Vaccination

Currently there is no commercially available GAS vaccine, though it has been widely pursued and was included as one of the priorities in the 2014 Global Vaccine Action Plan. There have been many roadblocks in finding a successful vaccine, including the large diversity of strains of GAS. Chiefly, vaccine developers have been targeting the M surface protein, but a recent approach has also used streptococcal pyrogenic exotoxins A and B (66) as well as another antigen, M-related protein, in the already existing multivalent M protein vaccines. (67) A phase 1 trial is being conducted of a 30-valent M protein vaccine in adults. (68) The governments of Australia and New Zealand, countries which harbor particularly high incidence of GAS-related disease, especially in indigenous populations, came together in 2014 to develop a Coalition to Advance New Vaccinations against group A *Streptococcus* (CANVAS). (69)

Evolving Resistance of GAS

Practitioners should be cognizant of the evolving resistance patterns of GAS to antibiotics other than penicillin. Several recent publications note fairly significant resistance to macrolides and clindamycin. One such study in Wisconsin demonstrated resistance to azithromycin in 15% of isolates from primary care clinics. (70)(71)(72) This emphasizes the importance of penicillins as the preferred antimicrobial and should be avoided only in definite penicillin allergy. In streptococcal pharyngitis, azithromycin may be used, but culture sensitivities should be obtained to ensure susceptibility. In addition, in invasive GAS, clindamycin should not be used alone but in combination with a β-lactam because 4% to 8% of GAS strains are resistant to clindamycin.

Carrier State

Children harboring GAS in the pharynx without clinical symptoms of disease are said to be carriers. A meta-analysis in 2010 estimated the prevalence of GAS carriage at about 12%. (6) GAS carriers are typically not infectious and the colonizing bacteria are less virulent. Colonized GAS is unlikely to become pathologic in the host or result in nonsuppurative complications. In general, antibiotic therapy is not recommended to eradicate the carrier state. Thus, if a throat swab is positive for GAS, but the patient lacks symptoms of streptococcal pharyngitis, treatment is not recommended. In the same vein, "proof of cure" after treatment of streptococcal pharyngitis is not recommended unless symptoms persist. Eradication may be considered in select situations, such as a community outbreak of PSGN or ARF, or a family history of ARF. Antibiotic options for eradication include 10 days of clindamycin, penicillin and rifampin, and amoxicillin/clavulanic acid. (12)(29)(73)

Prophylaxis

The only indication for GAS prophylaxis with robust evidence is for ARF and may consist of monthly intramuscular benzathine penicillin G or daily oral penicillin, or for penicillin-allergic patients, sulfisoxazole or a macrolide (see section on ARF for more details). (12)(29) Some clinicians may choose to provide prophylaxis to certain high-risk close contacts of patients with invasive GAS disease. These include people who are 65 years of age or older, those who are immunocompromised (eg, human immunodeficiency virus–positive individuals), or those with diabetes mellitus. Prophylaxis is not recommended in schools or child-care facilities. (29) Prophylaxis may consist of benzathine penicillin G, clindamycin, or azithromycin. (76) Finally, some physicians may choose to provide penicillin prophylaxis to patients with frequent PANDAS exacerbations; this decision should be made on a case-by-case basis because the evidence is not robust. Table 3 lists antibiotic indications and dosages.

Summary

- Group A *Streptococcus* (GAS) infections are highly prevalent, and account for major morbidity and mortality worldwide, from both primary infections and subsequent complications.
- On the basis of strong research evidence, all children older than 3 years who present with pharyngitis without features that strongly suggest a viral etiology should undergo testing for GAS pharyngitis, with negative rapid antigen detection tests followed by a throat swab culture. Posttreatment diagnostics are not recommended. (8)
- Diagnosis of acute rheumatic fever (ARF) should be made using the updated 2015 Jones criteria, which now include separate criteria for low- and moderate- to high-risk populations. Based on research evidence and consensus, echocardiography should be performed in all cases of suspected or confirmed ARF, even in the absence of auscultatory findings. (20) On the basis of strong research evidence, prophylaxis is recommended for patients with well-documented histories of rheumatic fever. (12)
- Based on strong research evidence, topical therapy with mupirocin or retapamulin is appropriate for localized impetigo, whereas numerous lesions or an outbreak situation should be treated with oral therapy. On the basis of research and observational studies, treatment of cellulitis without systemic involvement should target streptococci. On the basis of consensus, physicians may choose to treat cellulitis with systemic symptoms with an agent that covers methicillin-resistant *Streptococcus aureus.* (34)
- On the basis of expert consensus and observational studies, antimicrobial choice for acute necrotizing fasciitis should include a β-lactam antibiotic with clindamycin to mediate toxin GAS toxin. Vancomycin should also be added initially to cover methicillin-resistant *S aureus* until cultures are complete. (29)

References for this article are at http://pedsinreview.aappublications.org/content/39/8/379.

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1. A previously healthy 10-year-old boy is brought to the office in March with a sore throat that he has had for the past day. He has had fever at home up to 101.8°F (38.7°C). He has not had a cough or congestion. He had taken amoxicillin 4 months ago for acute bacterial sinusitis. He has no known allergies to medication. On examination he is awake and alert. Vital signs are normal except for an oral temperature of 101.5°F (38.6°C). There is an exudative pharyngitis with mildly tender anterior cervical adenopathy. The remainder of his examination findings are normal. Which of the following is the most appropriate next step in management?
   - A. Intramuscular ceftriaxone.
   - B. Oral azithromycin.
   - C. Oral penicillin.
   - D. Nasopharyngeal swab for viral multiplex polymerase chain reaction assay.
   - E. Throat swab for group A *Streptococcus* antigen.
2. A previously healthy 8-year-old girl is brought to the office with a 2-day history of fever and sore throat. She has not had a cough, vomiting, or diarrhea. When she was 1 year of age, she had had a rash after taking amoxicillin for 5 days, which had been prescribed for acute otitis media. She did not have respiratory distress when she had the rash. On physical examination her temperature is 101.2°F (38.4°C). There is an exudative pharyngitis with bilateral anterior cervical adenopathy. A rapid antigen detection test from a throat swab is positive for group A *Streptococcus.* Which of the following is the most appropriate treatment?
   - A. Azithromycin.
   - B. Ceftriaxone.
   - C. Cephalexin.
   - D. Clindamycin.
   - E. Trimethoprim-sulfamethoxazole.
3. A 7-year-old girl is admitted to the hospital with a 3-day history of joint pain and swelling of her knees, ankles, and wrists. It started with her left knee and then moved to her right ankle, right knee, and both wrists. The pain is significantly improved with ibuprofen. She has also had fever, with temperatures ranging from 101°F to 102°F (38.3°C–38.8°). She had a sore throat when she was with her family on a spring break vacation 2 to 3 weeks ago, which resolved after 3 days without any antimicrobial therapy. Currently on physical examination she has swelling and pain of her right knee, right ankle, and both wrists. There is no murmur on cardiac examination. Her physical examination findings are otherwise normal. Her C-reactive protein is 50 mg/L (476 nmol/L) and erythrocyte sedimentation rate 85 mm/hr. ASO and anti-DNASE B antibody levels are significantly elevated. Electrocardiography shows prolonged PR interval. In addition to starting naproxen and oral penicillin, which of the following is the most appropriate next step in management?
   - A. Brain magnetic resonance imaging.
   - B. Cardiac magnetic resonance imaging.
   - C. Echocardiography.
   - D. Intravenous immunoglobulin.
   - E. Pulse methylprednisolone.
4. A previously healthy 3-year-old boy is brought to the emergency department because of perianal itching and pain with defecation. He has not had fever. His review of systems is otherwise negative. On examination there is sharply demarcated 3 to 4 cm circumferential erythema around his anus. He has no known drug allergies. Which of the following is the most appropriate next step in management?

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    A. Oral clindamycin.
    B. Swab of the perianal area for culture.
    C. Throat swab for culture.
    D. Throat swab for group A *Streptococcus* antigen.
    E. Topical neomycin.

5. A 14-year-old boy is brought to the emergency department with fever and a very painful right thigh. Three days ago, he developed what appeared to be a bug bite on his right thigh and then the area of redness increased. Over the past day he has had fever with worsening pain in his thigh. Now the area has started to become purple and there are blisters. He also seems confused. On examination his temperature is 102°F (38.8°C). He has tachycardia and his blood pressure is 118/76 mm Hg. Palpation of the right thigh has a hard, wooden feel that extends beyond the area of erythema. There is purplish discoloration centrally with 2 bullae. He is going to the operating room for debridement. He has no known allergies. In addition to starting intravenous fluids, piperacillin/tazobactam, and vancomycin, which of the following is the most appropriate management?

    A. Computed tomography with contrast of the thigh.
    B. Fresh frozen plasma transfusion.
    C. Intravenous clindamycin.
    D. Intravenous immunoglobulin.
    E. Intravenous metronidazole.

Pediatric Esophageal Disorders: Diagnosis and Treatment of Reflux and Eosinophilic Esophagitis

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Education Gaps

Gastroesophageal reflux (GER) occurs frequently in infants, with gastroesophageal reflux disease (GERD) representing only a small fraction of affected patients. The number of prescriptions for proton pump inhibitors (PPIs) has significantly increased. Clinicians need to be aware of the paucity of data supporting the effectiveness of PPIs for treating infants with reflux, and possible adverse effects of PPIs. Clinicians should also be able to recognize the potentially similar clinical presentation of GER and eosinophilic esophagitis.

Objectives After completing this article, readers should be able to:

1. Differentiate physiologic reflux from gastroesophageal reflux disease (GERD).
2. Understand that an upper gastrointestinal (UGI) study should not be ordered for diagnosing reflux.
3. Recognize the limitations of PPI medications.
4. Know possible clinical presentations of eosinophilic esophagitis (EoE).
5. Identify dietary and medication treatment options for EoE.
6. Be cognizant of other esophageal disorders that can cause esophageal dysfunction.

Abstract

Gastroesophageal reflux (GER) occurs frequently in infants, generally at its worst at 4 months of age, with approximately two-thirds of infants spitting up daily. GER typically improves after 7 months of age, with only ~5% of infants continuing to have reflux at 1 year of age. The diagnosis can often be made based on clinical symptoms. Upper GI (UGI) study has low sensitivity and specificity and should not be ordered as a diagnostic test for reflux. UGI study is best for evaluating other anatomic causes of vomiting. GER becomes problematic

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ABBREVIATIONS

BRUE	brief resolved unexplained event
EoE	eosinophilic esophagitis
FDA	Food and Drug Administration
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
H2RA	histamine-2 receptor antagonists
PPIs	proton pump inhibitors
TLESR	transient lower esophageal sphincter relaxations
UGI	upper gastrointestinal

gastroesophageal reflux disease (GERD) when complications are present, including feeding difficulties and poor weight gain. Conservative treatment and thickened formula can be helpful for treating GERD. Proton pump inhibitors (PPIs) are frequently prescribed for treating reflux. However, studies do not show a definite benefit in infants, and there are potential side effects. Older children with GERD may present with regurgitation, heartburn, chest discomfort, dysphagia, abdominal pain, vomiting, poor appetite, or poor weight gain. Upper endoscopy is considered for children with concerning symptoms, persistent symptoms despite treatment, and relapse of symptoms after treatment. Other esophageal disorders can have a similar clinical presentation as GERD, notably eosinophilic esophagitis (EoE). EoE is a chronic immune-mediated disorder of the esophagus, which may present as dysphagia, food impaction, heartburn, vomiting, abdominal pain, feeding difficulties, or failure to thrive. Diagnosis is made histologically by the presence of esophageal eosinophilia on endoscopic biopsies in the correct clinical setting.

GASTROESOPHAGEAL REFLUX IN INFANTS

Definitions

Gastroesophageal reflux (GER), also referred to as spitting up, regurgitation, and spilling, is defined as the passage of contents from the stomach up into the esophagus. When GER causes troublesome symptoms or complications, including significant irritability, feeding difficulties, or poor weight gain, it is named *GERD*.

Prevalence and Natural History

GER is a normal physiologic process that occurs in healthy infants and children. A cross-sectional survey of 948 parents of healthy children found that reflux is at its worst at 4 months of age; at this time, about two-thirds of infants are spitting up at least once a day. (1) Similarly, another study reported that 41% of 3- to 4-month-old infants are spitting up at least half of their feeds every day. (2) Reflux improved after 7 months of age, at which time the percentage of infants spitting up on a daily basis dropped to ~20%, which further improved to ~5% or less by 1 year of age. (1)(2) This improvement is likely related to a combination of factors, including starting infant foods, spending more time in the upright and sitting positions, and decreased number of lower esophageal sphincter relaxations.

Certain pediatric populations are at higher risk for reflux, including children with hiatal hernia, neuromuscular disorders, chronic respiratory disorders, prematurity, history of esophageal atresia, achalasia or other reason for esophageal dysmotility, and obesity. There also appears to be a genetic component to reflux, as noted by an increase in reflux symptoms and reflux-associated diseases within families. (3)(4)

Pathophysiology

GER occurs secondary to transient lower esophageal sphincter relaxations (TLESR). These TLESR occur more often in the postprandial period, in response to gastric distention. Gastric distention and increases in intragastric pressure increase the number of TLESR, allowing GER to occur more frequently after eating and after eating larger meals. (5)

The antireflux barrier consists of the diaphragmatic crural support, the intra-abdominal segment of the esophagus, and the angle of His. In patients with a sliding hiatal hernia, these protective barriers are compromised. In these patients, the gastric cardia is displaced upward above the diaphragmatic hiatus. This interferes with the crural diaphragm support to the lower esophageal sphincter, thus increasing the potential for reflux. (6) An abnormal esophageal peristalsis response to refluxed material can lead to impaired clearance and reflux-related complications. (7)

Clinical Signs and Symptoms

GER often presents as effortless spitting up after feeds and in between feeds. At times, reflux can trigger more forceful vomiting, probably due to refluxed gastric contents stimulating pharyngeal sensory afferents. (8) Infants with GER may be “happy spitters,” and others may be fussy. Both reflux and fussiness occur commonly in infants; however, a double-blind placebo-controlled crossover trial of omeprazole in irritable infants with GER failed to demonstrate a correlation. Compared with placebo, omeprazole treatment resulted in improvement in the reflux index on pH study, but “there was no significant difference in the cry/fuss time while taking either omeprazole or placebo.” Both groups showed improvement in irritability with time, regardless of treatment. (9)

Sandifer syndrome is an uncommon, but specific manifestation that has been associated with GERD. Sandifer syndrome is described as dystonic spasmodic movements with head, neck, and back posturing. The etiology is not entirely clear, but may be related to shared innervation of the diaphragm and muscles associated with movements of the head and neck, with diaphragmatic stimulation then causing reflex contraction of these muscles. (10) Another possible explanation could be that these movements result in symptomatic relief, perhaps related to improvement in esophageal motility. (11)

Infants with GERD may have associated feeding problems. These infants may associate reflux-related discomfort with feeding times, possibly progressing to feeding aversion. They may not gain weight well, due to both poor intake and regurgitation of consumed feeds.

GERD as a cause of brief resolved unexplained events (BRUEs) has been studied; these events were previously referred to as *apparent life-threatening events*. Data to support an association of reflux with BRUEs are limited. In a prospective infant study, simultaneous pneumogram and impedance pH study showed that only ~15% of 527 apneic episodes were temporally linked with reflux.(12) “The available evidence suggests that in the vast majority of infants, GER is not related to pathologic apnea or to apparent life-threatening events, although a clear temporal relation based on history, observation, or testing occurs in individual infants.”(8) In select infants who do have GERD-associated apnea or BRUE, this could be explained as an exaggeration of the normal protective reflexes that inhibit breathing when there is fluid in the pharynx. In the cases in which reflux is the cause of BRUE, this is more likely when the event occurred in close proximity to a feed, the infant was awake, and obstructive apnea was present. (8)

Diagnosis and Evaluation

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition published updated clinical practice guidelines in March 2018, to provide recommendations for the diagnosis and management of GER and GERD in infants and children. (13) Most often, GER can be diagnosed based on clinical history, without any additional testing. Concerning signs and symptoms that would warrant evaluation for other causes of vomiting include bilious vomiting, consistently forceful vomiting, failure to thrive, hematemesis or hematochezia, fever, lethargy, hepatosplenomegaly, bulging fontanelle, macro/microcephaly, hypo/hypertonia, seizures, suspected metabolic syndrome, and onset of vomiting after 6 months of age, among others. (8) Other diagnoses can present with refluxlike symptoms, including milk protein intolerance and EoE. Infants with milk protein intolerance improve with protein hydrolysate or elemental formula, or with exclusion of milk from the maternal diet if breastfed. EoE is discussed in further detail herein.

It is important to understand that although a UGI study may show episodes of reflux, this study should not be ordered as a diagnostic test. (13) The sensitivity, specificity, and positive predictive value of a UGI study, using pH monitoring as the reference, ranges from 29% to 86%, 21% to 83%, and 80% to 82%, respectively. (8) The low sensitivity and specificity could be due to the brief fluoroscopy time, the higher density of barium contrast compared with normal gastric contents, and/or the high occurrence of physiologic reflux. Instead, the indication for a UGI study is to evaluate for hiatal hernia or other anatomic abnormality as the cause of vomiting, such as malrotation, stenosis, web, annular pancreas, etc. UGI study can also identify tracheoesophageal fistula, vascular rings, achalasia, and motility abnormalities.

Twenty-four–hour impedance pH study is a test that can evaluate for reflux, including the frequency of reflux episodes, acid versus nonacid reflux, the extent of reflux (episodes that reach the proximal esophagus), and correlation of reflux episodes with symptoms. This test detects intraluminal bolus movement between electrodes positioned in the esophagus. GER is characterized by a drop in impedance progressing distally to proximally as liquid advances from the stomach to esophagus. Impedance testing is typically combined with pH monitoring to determine if the GER is acidic or nonacidic. The study can be conducted with or without reflux medications and patients should receive their usual oral/bottle feeds and/or tube feedings during the study. This study requires special equipment and training, and may not be available at all medical centers.

Endoscopy is reserved for those patients who have a more concerning history or examination findings and/or fail to respond to usual treatments. Endoscopy may also be considered for persistent reflux symptoms after 18 to 24 months of age. Endoscopy can evaluate for reflux esophagitis and other causes of refluxlike symptoms, including EoE.

Studies that have not been found to be useful for diagnosing reflux include gastrointestinal scintigraphy (milk scan) and bronchoalveolar lavage to check for lipid-laden macrophages and pepsin. These tests have low sensitivity and specificity for diagnosing reflux. (8)(13)

Management

In otherwise healthy infants with reflux, lifestyle modifications, caregiver education, and reassurance may be all that is needed until the reflux improves on its own with time. Lifestyle modifications include smaller, more frequent feeds, frequent burping, keeping the infant upright after feeds, avoiding vigorous handling after feeds, elevating the head of the bed when sleeping, and avoiding tobacco smoke exposure. Reflux is less likely to occur in the prone position and left side down position (14); however, because of the instability of a side-lying position and the risk of sudden infant death syndrome in the prone position, the only recommended sleeping position is on the back. Although a car seat does help keep infants in a more inclined position, this could actually exacerbate reflux due to increases in intra-abdominal pressure. (15)

Thickeners, like commercial powder thickeners or infant cereal, can be added to formula to help decrease reflux episodes. Because most reflux events in infants are already nonacidic because milk/formula neutralizes gastric acid, thickening formula is a practical consideration for treating reflux. A systematic review and meta-analysis of 14 randomized controlled trials assessing the effect of thickened formula for GER in infants, showed that thickened formula significantly reduced the number of episodes of regurgitation and vomiting. However, esophageal pH monitoring showed no change in the reflux index (percentage of time during which the pH was <4) or the number of episodes of acid reflux per hour. The authors stated that "although the differences were statistically significant, the reduction may be of questionable clinical significance (eg, reduction in regurgitation by 0.6 episode per day)." (16)

Infant cereal (rice cereal and oatmeal cereal) and commercial powder thickeners can be used to thicken formula. However, recent concerns have been raised about increased levels of arsenic in rice cereal. Nectar consistency equals 1.5 teaspoons of cereal per ounce of formula. Adding infant cereal or commercial thickener powder increases the calorie density of the formula. Thickening formula typically requires a faster flow bottle nipple because of the increased effort required to suck the thicker formula. Pulverizing the cereal can decrease the potential for cereal clogging the nipple. Powder thickeners and infant cereals do not work well to thicken breast milk, because the enzymes in breast milk break down the thickener. Although xanthum gum–based thickeners can thicken breast milk, they are not recommended for infants younger than 1 year because of the potential association with necrotizing enterocolitis. (17) In May 2011, the US Food and Drug Administration (FDA) advised against using a commercial xanthum gum gel thickener in infants born before 37 weeks. Another option to thicken breastmilk is a carob bean gum thickener. Carob bean gum thickener must be added to warmed breastmilk for it to dissolve completely and thicken. It is marketed for use in infants older than 42 weeks' corrected gestational age and weighing more than 6 pounds.

Specific commercial formulas are available, which will thicken when consumed. One advantage of these formulas is that they do not require increased effort to suck from the bottle, because they become thickened once in the stomach and exposed to gastric acid. Therefore, these formulas are not very effective in infants receiving an acid-blocker medication. Formulas with higher whey percentage could also be beneficial for infants with GERD, because whey empties faster from the stomach than casein, resulting in less formula in the stomach to be refluxed. As noted earlier, because of the potential for milk protein intolerance possibly presenting with similar refluxlike symptoms, a 2- to 4-week trial of a protein hydrolysate or elemental formula is reasonable. (13)

Medications are often prescribed to treat GERD, including histamine-2 receptor antagonists (H2RAs) and PPIs. However, a number of studies show no decrease in infant regurgitation of PPIs compared with placebo. (13) Multiple studies have shown no significant difference in PPIs over placebo in improving crying or irritability, making it uncertain whether PPIs provide a definite benefit. (13)

Antacids should be used with caution in infants, based on reports of increased plasma aluminum levels or milk alkali syndrome with repeated use. (18) H2RAs decrease acid secretion by inhibiting the H2 receptor on the gastric parietal cell. H2RAs work quickly, with gastric pH rising within 30 minutes and peak onset of action about 2.5 hours after dosing. PPIs suppress acid production by inhibiting the H^+K^+ ATPase on the gastric parietal cell, the final step in acid production. The onset of action of PPIs is 1 to 2 hours, with peak effect being seen after several days. Compared with H2RAs, PPIs have higher rates of improvement in healing erosive/ulcerative esophagitis. (19) PPIs are able to inhibit meal-induced acid secretion, with best bioavailability seen when administered 30 minutes before meals. Tachyphylaxis, or tolerance, can develop quickly with oral and intravenous H2RAs. (20)(21) PPIs have not been shown to develop tachyphylaxis.

The number of prescriptions for PPIs has significantly increased. "Use of PPIs increased 4-fold from 2000 to 2003" in infants younger than 12 months. (22) PPI options include omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, and dexlansoprazole. The FDA has approved omeprazole, lansoprazole, and rabeprazole for infants older than 1 year, pantoprazole for children older than 5 years, and dexlansoprazole for those older than 12 years. Only esomeprazole is approved for infants older than 1 month.

PPIs can be prescribed as liquid suspensions, packets, soluble tablets, or capsules. The capsules contain enteric-coated granules and can be opened up and sprinkled on a spoonful of soft food, like applesauce or yogurt, or added to 2 oz of apple juice. The soluble tablets can be placed on the tongue to dissolve or they can be dissolved in 5 to 10 mL of water before administration. Choice of PPI often depends on insurance formulary and ease of administration. Dosing for PPIs generally starts at 1 to 1.5 mg/kg per day. PPIs are dosed starting at once daily, though can be increased to twice daily if needed. Twice-daily dosing has shown faster improvement in symptoms at 1 week, but with a similar response at 2 weeks. (23)

Adverse effects of H2RAs and PPIs are uncommon and similar to placebo, including headache, diarrhea, abdominal pain, and nausea. (24)(25)(26)(27) A randomized double-blind placebo-controlled study of infants with GER treated with lansoprazole found that compared with placebo, there was no difference in the number of infants who responded to lansoprazole treatment; however, there was an increased number of adverse events in the lansoprazole-treated infants, including lower respiratory tract and lung infections. (28) A different prospective study showed that children with GERD who were treated with ranitidine or omeprazole had increased rates of acute gastroenteritis and community-acquired pneumonia compared with healthy controls. The increased risk of infections seen in children treated with acid-suppressing medications could be related to changes in intestinal flora, direct inhibitory effect of acid-suppressing medications on leukocyte functions, and/or absence of the low gastric pH limiting microbial survival. (29) Some adult studies have raised concern about PPIs causing increased risk for osteoporosis and fractures, but other studies have found no increased risk in patients without other major risk factors. (30) PPI use alone does not seem to be a risk factor for hypomagnesemia. (31)(32) Some studies show an association of PPIs with iron-deficiency anemia. (33)(34) However, many of these adult studies are confounded by other comorbidities. (13)

Erythromycin and metoclopramide are prokinetic medications that can increase gastric emptying, thereby potentially decreasing reflux episodes. However, data supporting the use of prokinetic medications for treatment of reflux are insufficient, and also these medications carry the potential for adverse effects and drug-drug interactions. (35) There is a black box warning for metoclopramide for tardive dyskinesia, characterized by repetitive potentially irreversible involuntary movements of the body, most often the face. Other side effects of metoclopramide include restlessness, irritability, lethargy, headache, confusion, difficulty sleeping, gynecomastia, and galactorrhea. Erythromycin has the potential to cause gastrointestinal symptoms, including abdominal pain, nausea, vomiting, diarrhea, and loss of appetite. Also, an association has been found between erythromycin and prolongation of the QT interval and torsade de pointe arrhythmia. Erythromycin should not be given with other drugs that can prolong the QT interval or drugs that are metabolized by P450 enzymes. Given the lack of strong data and the potential for adverse effects, prokinetic medications are not recommended for routine treatment of children with reflux. (8)(13)

Ultimately, for patients with life-threatening complications proven to be related to GERD, surgical treatment with Nissen fundoplication can be considered. Nissen fundoplication is not indicated in infants with frequent spitting up who are otherwise feeding well and gaining weight well, because infants with uncomplicated GER are expected to improve on their own with time. In these patients, potential complications of Nissen fundoplication outweigh the benefits. Possible post-Nissen complications include dumping syndrome, gas bloat syndrome, early satiety, and postoperative retching and gagging. One study reported ∼75% of 233 pediatric patients were restarted on antireflux medications within 1 year after a Nissen procedure. (36)

Prognosis

Infants with GER should improve with time. There is often a dramatic improvement in reflux symptoms after 7 months of age, with only a small percentage of infants still having problems with reflux at 1 year of age. Referral to a pediatric gastroenterologist should be considered if concerning symptoms are present, like hematemesis, feeding difficulties, poor weight gain, and respiratory symptoms, and/or the reflux does not improve with time.

Reflux in Older Children

Reflux and heartburn symptoms are reported to occur weekly in ∼2% of 3- to 9-year-old children and 5% to 8% of 10- to 17-year-old children. (37) Children with more frequent spitting up episodes during infancy were 2.3 times more likely to have 1 or more reflux symptoms at 9 years of age. (2) Older children with reflux may present with regurgitation, heartburn, vomiting, poor appetite, poor weight gain, chest discomfort, dysphagia, and/or abdominal pain, often after mealtimes. Less commonly, respiratory and ear-nose-throat symptoms, like wheezing, hoarseness, or cough, could be a presentation of reflux.

There does appear to be an association between GER and asthma. The number of abnormal esophageal pH studies is increased in children with asthma. (38)(39)(40) Reflux could worsen asthma symptoms, but asthma could also worsen reflux symptoms. Mechanisms by which asthma could worsen reflux includes cough-induced increases in intra-abdominal pressure, lung hyperinflation changing the relation between the crural diaphragm and the gastroesophageal junction, airway obstruction causing negative intrathoracic pressure, and asthma medications decreasing the lower esophageal sphincter pressure. Reflux as the cause of worsening asthma symptoms could be secondary to aspiration of gastric contents resulting in airway inflammation and airway hyperresponsiveness. Respiratory and gastrointestinal systems also have a common embryologic origin, resulting in shared innervation by the vagus nerve and shared autonomic reflexes. Reflux could stimulate receptors in the distal esophagus and lead to vagal reflex and bronchial constriction. The association of reflux with asthma appears to be greater when the asthma is difficult to control, when reflux symptoms have an onset before respiratory symptoms, and when there are nocturnal asthma symptoms. It is recommended that asthmatic children with these specific symptoms be considered for baseline pulmonary function tests followed by a 3-month trial of empiric acid suppression medication. (41)

Although some studies have shown an association of reflux with specific respiratory and ear-nose-throat diagnoses, others have not shown such an association. (40)(42)(43)(44) Pneumonia is not often caused by aspiration of refluxed contents. Recurrent pneumonia could be related to abnormal swallowing; therefore, these children should undergo a video swallow study to evaluate for aspiration of swallowed liquids, rather than assuming that the pneumonia is secondary to reflux and only initiating reflux treatments. Ultimately, neither the association of respiratory symptoms with reflux nor the response to reflux medications has been established by controlled studies, and other causes of these symptoms should be assessed. Although some studies have shown an association of dental erosions with GERD, other studies have not shown such an association. (45)(46) Recommendations for specific evaluation and length of treatment are unclear. Close follow-up with a pediatric dentist is important.

It is important to also consider unrecognized constipation contributing to reflux symptoms. This could be explained by the cologastric brake, where stool loading in the rectum activates a rectogastric inhibitory reflex. (47) Constipation can cause delayed gastric emptying and this gastroparesis can result in reflux. Studies show that gastric emptying improves after starting treatment with stool softeners. Treatment of constipation has the potential to quickly resolve chronic upper gastrointestinal symptoms, including reflux. (48)

Treatment for reflux in older children includes lifestyle modifications and weight management, if overweight. Sleeping with the head of the bed elevated and not lying down right after eating can be helpful; avoiding caffeinated beverages, chocolate, peppermint, and spicy foods can also be beneficial. Ideally patients should limit fatty foods, because fat can slow gastric emptying, thereby increasing the possibility for reflux. It is also better to eat smaller portions, because smaller meals decrease TLESR. Avoiding tobacco exposure and alcohol is important, as these can decrease lower esophageal sphincter pressure, increasing the risk for reflux events. Several studies have shown that chewing sugarless gum can increase salivary flow and neutralize acid, thus helping with reflux symptoms (49)(50)(51); however, the sorbitol sweetener in excessive amounts of sugarless gum could contribute to abdominal pain and diarrhea.

Antacid medications neutralize acid and are appropriate for short-term relief of occasional reflux symptoms. They work within 5 minutes and have a short duration of effect. PPI medications can be used to empirically treat classic reflux symptoms in older children, starting at a dose of 1 to 1.5 mg/kg per day. Patients who do not respond to once-daily dosing can be given twice-daily dosing (generally 1 mg/kg per dose twice a day up to 40 mg twice a day). If symptoms improve with acid-suppressing medications, recommendations are to continue treatment for 4 to 8 weeks and then wean. (13) It is better to wean the medication rather than stop suddenly, to avoid rebound hyperacidity caused by increased serum gastrin levels associated with longer-term PPI use. If concerning symptoms are noted at the time of presentation, symptoms persist despite empiric PPI treatment, or a quick relapse of symptoms is seen after PPI treatment, endoscopy should be considered for further evaluation, including reflux esophagitis and EoE.

EOE IN CHILDREN

Definition

EoE belongs to a group of disorders known as eosinophilic gastrointestinal disorders. EoE is a chronic immune-mediated disorder of the esophagus characterized by clinical symptoms of esophageal dysfunction and the histologic presence of more than or equal to 15 eosinophils per high-powered field in the esophageal mucosa, in the absence of other eosinophilic syndromes. (52)

Prevalence

EoE is a relatively recently identified disease with the first adult report in 1978 (53) and the first pediatric report in 1983. (54) Although some studies have suggested an increase in the prevalence of EoE, a review of esophageal biopsies from 1980 to 1988 compared with 2001 to 2002 showed that the prevalence of EoE was unchanged. (55) Recently, the incidence and prevalence of EoE in children was found to range from 0.7 to 10 in 100,000 per person-year and 0.2 to 43 in 100,000, respectively. (56) Prevalence of disease was highest in those children with dysphagia or food impaction, at 63% to 88%. (56) EoE affects male patients disproportionately, with a male-to-female ratio of approximately 3 to 1. (57) Historically, EoE was thought to preferentially affect white patients; however, recent studies suggest similar frequency in white and black children. (58) EoE has been reported in male and female patients of all age groups and of most ethnicities and races. The overall risk for first-degree relatives of a patient with EoE is 1.8%, increasing to 2.3% for sex-matched first-degree relatives. (59)

Clinical Signs and Symptoms

Clinical symptoms of EoE are variable and often age dependent. Symptoms in the younger child may include regurgitation, nausea, vomiting, or feeding difficulties, and may be severe enough to cause failure to thrive. In the older child and adolescent, symptoms of dysphagia, heartburn, food impaction, nighttime cough, and epigastric abdominal pain are more common. Other possible symptoms of EoE in both age groups include malnutrition, growth failure, esophageal dysmotility, and rarely, hematemesis. Asking the key questions of whether the child chews food excessively or uses liquid chasers during meals may help identify clinical symptoms of EoE, which parents may mistakenly attribute to simply “eating too fast.” It is also necessary to consider EoE in the child with chronic heartburn or GERD given its potentially similar clinical presentation. A personal history of atopy manifesting as asthma, eczema, allergic rhinitis, and/or food allergies is reported in up to 60% of children with EoE, and can be another clue to the underlying diagnosis. (60)(61) Children with symptoms of possible EoE should be referred to a pediatric gastroenterologist for evaluation, particularly those who have dysphagia, food impaction, reflux symptoms unresponsive to PPI, longstanding reflux symptoms, or inability to withdraw PPI therapy without recurrence of symptoms.

Pathophysiology

Both genetic and environmental factors are implicated in the pathogenesis of EoE. EoE is believed to be caused by non–immunoglobulin E allergic response to allergen(s). Allergens are most frequently foods, though some research supports environmental aeroallergens as potentially causative. (62) An EoE genetic susceptibility locus has been identified at 5q22, demonstrating a genetic basis to this disorder. (63) More recently, 2 genome-wide association studies have discovered an association of the 2p23 locus with EoE. (64)(65) It is believed that when a food allergen enters the body through a disrupted epithelial barrier, esophageal antigen–presenting cells interact with the allergen, releasing a cascade of proinflammatory cytokines and chemokines, leading to the recruitment of eosinophils to the esophagus. (66)

Diagnosis

EoE is an endoscopic diagnosis in the correct clinical setting. Ideally, when a diagnosis of EoE is being entertained, the patient should be started and maintained on a PPI for a period of 6 to 8 weeks before endoscopy. Endoscopic visual clues to diagnosis include linear furrows, concentric rings, loss of the typical esophageal vascular pattern, and/or the presence of white patches on the mucosal surface (Figs 1–3). However, up to 30% of patients may have a visually normal-appearing esophagus, highlighting the importance of a biopsy in making the diagnosis of EoE. (67)

PPI use before endoscopy is recommended to rule out GERD as the cause of esophageal eosinophilia, and also attempt to identify those patients with an entity known as PPI-responsive esophageal eosinophilia. In these patients, esophageal eosinophils normalize after PPI use. PPI-responsive esophageal eosinophilia may represent a distinct clinical disorder, possible subtype of EoE, or severe GERD. (68)

Multiple biopsy specimens should be obtained from both the distal and proximal esophagus, because EoE can be a patchy disease. A count of more than or equal to 15 eosinophils per high-powered field must be present on and isolated to the esophageal biopsy specimen; biopsy specimens from

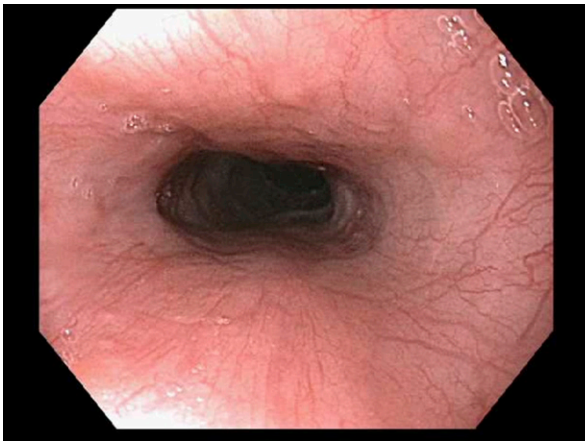


Figure 1. Endoscopic appearance of normal esophagus.

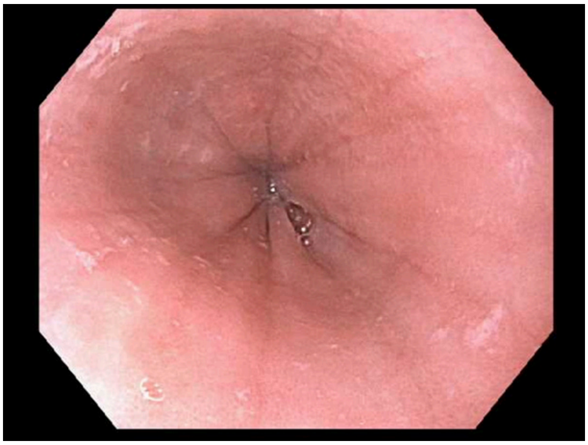


Figure 2. Mucosal edema, loss of vascular pattern, and linear furrows in a patient with eosinophilic esophagitis.

the stomach and duodenum should be devoid of excessive eosinophils. Excessive eosinophils in the stomach and/or duodenum would suggest the alternate diagnosis of eosinophilic gastritis or eosinophilic gastroenteritis. Currently, EoE remains an endoscopic diagnosis; there are no diagnostic radiologic, serologic, or stool studies.

Treatment

EoE is managed with dietary therapy, medical therapy, or combination of both. Systemic steroids such as prednisone should not be used routinely or long term in the treatment of EoE given their significant side effect profile. However, systemic steroids could be considered in the short-term management of the patient with acute conditions such as severe dysphagia, narrow esophagus, or poor growth. Current medical treatment of EoE includes the use of swallowed topical corticosteroids: fluticasone proprionate or oral viscous budesonide. Fluticasone is puffed into the mouth and then swallowed. Budesonide is often mixed with sucralose to make a viscous solution before swallowing; amino acid–based nutritional powders are another option to thicken budesonide. Instructions include not eating or drinking for 30 minutes after medication administration, and then rinsing the mouth with water. When swallowed, these topical corticosteroids are deposited along the surface of the esophageal mucosa, with the goal being symptom resolution and histologic improvement. Dosing for these medications is based on age and weight, and ranges from 88 to 440 μg twice daily for fluticasone proprionate and 0.5 to 1 mg twice daily for budesonide. Potential side effects include dry mouth, nosebleed, and oropharyngeal or esophageal candidiasis. Although previously no significant systemic side effects were seen with topical corticosteroids, newer studies have shown some evidence of adrenal suppression with the use of swallowed fluticasone and oral viscous budesonide. (69)(70) Of patients treated with swallowed topical corticosteroids, 50% to 85% show improvement in their EoE symptoms. (71)(72)(73)(74) However, multiple studies demonstrate that EoE almost always returns after discontinuation of therapy if no other interventions have been instituted. (60)(75)(76)

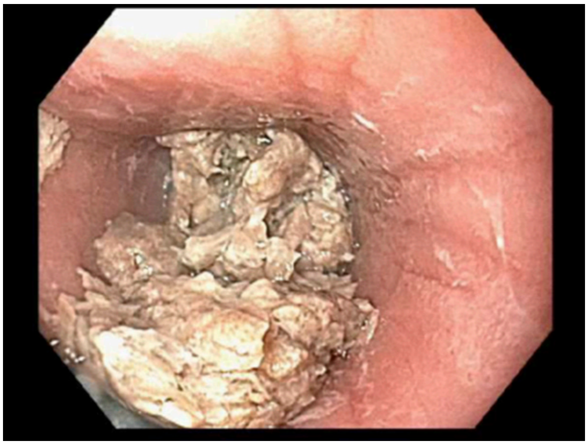


Figure 3. Food impaction in a patient with eosinophilic esophagitis.

Dietary modification is an important treatment arm in the care of the patient with EoE. Dietary modifications include the use of an amino acid–based elemental diet, empiric elimination of the 6 most common food allergens (milk, soy, eggs, wheat, nuts/peanuts, fish/shellfish) referred to as the 6-food elimination diet, or the selective elimination of specific foods based on results of allergy testing and clinical symptoms. Elimination of dietary allergens has proven successful in improving clinical symptoms and histology.

More than 95% of patients treated with exclusive amino acid–based elemental formula demonstrate clinical and histologic improvement. (60)(77) Endoscopy is repeated a minimum of 6 weeks after dietary or medication change. Clinical symptoms do not always correlate with histologic findings, making endoscopic surveillance important. Once endoscopic resolution of esophageal eosinophilia is noted, foods can be systematically reintroduced while monitoring for the redevelopment of clinical symptoms; endoscopy is used to ensure that there is no histologic evidence of disease recurrence in the absence of clinical symptoms. Although an elemental diet has excellent success in treating EoE, consuming the volume of formula needed to maintain nutrition may be a real challenge, and a nasogastric or gastrostomy tube may be required.

Approximately 75% of patients demonstrate improvement with empiric elimination of the 6 most common food allergens. (78) This 6-food elimination diet does not require any food allergy testing. However, it has a number of potential drawbacks, including the unnecessary elimination of foods leading to more significant dietary restriction and the need for repeated endoscopies to ensure that the reintroduced foods did not cause relapse of the EoE. Empiric elimination of milk alone could be considered, because milk is the most common food identified as a cause of EoE, and studies have shown that eliminating milk can successfully treat EoE, even when food allergy test results are negative. (79) The guided food elimination diet, in which foods are eliminated based on allergy testing and clinical reactions, has success rates of 57% to 77%. (60)(80) Newer dietary approaches include the 4-food elimination diet (milk, wheat, eggs, and legumes), and the 2-food elimination diet (animal milk and gluten-containing cereals) with "step-up" to the 4-food elimination diet or 6-food elimination diet in nonresponders. (81)(82) The treatment of EoE, whether dietary elimination and/or swallowed topical corticosteroids, is a decision that must be individualized for the patient, taking into account the present symptoms and patient/family compliance.

Dilation therapy is reserved for patients with esophageal stricture. Dilation may be achieved via the passage of sequentially larger bougie dilators or endoscopic balloon dilators. Esophageal perforation is a possible and serious potential complication of dilation therapy. In pediatrics, medication or dietary treatment is typically the first treatment choice.

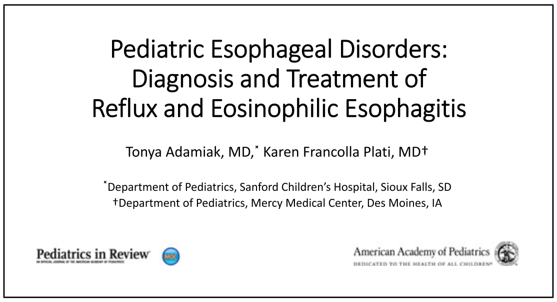
Other Esophageal Disorders

Esophageal dysfunction can also result from a myriad of anatomic, traumatic, iatrogenic, and motility causes. Congenital anatomic abnormalities of the esophagus include congenital esophageal stenosis, esophageal atresia with or without fistula, and vascular rings, among others. Caustic ingestions from household cleaners are particularly dangerous given their markedly alkaline nature; perforation, mediastinitis, and/or stricture may result. Pill esophagitis has been associated with a number of medications, including tetracycline and other acne medications, as well as nonsteroidal anti-inflammatory drugs. Ingestion of foreign bodies is a common problem in children, with more than 100,000 cases occurring annually; the cervical esophagus, the level of the aortic arch, and the lower esophageal sphincter are the 3 most likely areas of esophageal impaction. Esophageal damage from a button battery lodged in the esophagus can be very severe and burns may occur in as little as an hour after ingestion, necessitating prompt endoscopic removal. Achalasia is a motor disorder of the esophagus characterized by lack of esophageal peristalsis, increased lower esophageal sphincter pressure, and incomplete relaxation of the lower esophageal sphincter; it presents clinically as a functional obstruction in the region of the esophagogastric junction. Together, these diagnoses account for many of the other causes of esophageal dysfunction and disease. (83)

Summary

- Based on strong research evidence, upper gastrointestinal (UGI) study should not be ordered as a diagnostic test for reflux, because the sensitivity and specificity are low. UGI study is, however, helpful to evaluate for anatomic abnormalities that could cause vomiting. (8)(13)
- Based on some research evidence as well as consensus, proton pump inhibitors (PPIs) are not expected to improve reflux symptoms or fussiness in infants. There is also concern about possible adverse effects related to PPIs, including pneumonia and gastroenteritis. (8)(9)(13)(28)
- Based primarily on consensus due to lack of relevant clinical studies, eosinophilic esophagitis should be considered in the child with gastroesophageal reflux disease given its potentially similar clinical presentation.
- Based on strong research evidence, eosinophilic esophagitis should be managed with dietary therapy, medical therapy, or combination of both. (60)(71)(72)(73)(74)(77)(78)(79)(80)(81)(82)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/8/392.supplemental.



Pediatric Esophageal Disorders:
Diagnosis and Treatment of
Reflux and Eosinophilic Esophagitis

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1. A 2-month-old boy is brought to the clinic by his parents because of persistent vomiting for the past 2 weeks. The mother thinks that the child might be vomiting green occasionally. The child has not had significant weight gain since the last time you saw him at 2 weeks of age. On physical examination, he is less than the 5th percentile for weight. You are concerned that the child may have some underlying anatomic condition. Which of the following is the most appropriate next step in diagnosis in this patient?
   A. 24-hour impedance pH study test.
   B. Surgery consultation.
   C. Ultrasonography of the abdomen.
   D. Upper gastrointestinal series.
   E. Radiography of the abdomen.
2. You are seeing a 3-month-old boy in your clinic. The mother reports that he has been "vomiting with every feed" and she is concerned that he is "not keeping down anything." He is taking a regular cow milk–based formula. On physical examination, he is an alert, active infant with stable and normal vital signs. The infant is growing well and has been at the 75th percentile for height and weight on the growth curve. The remainder of the physical examination findings is unremarkable. Which of the following is the most appropriate next step in management for this patient?
   A. Follow-up in 1 week for weight check.
   B. Prescribe acid suppressants.
   C. Pyloric ultrasonography.
   D. Reflux precautions.
   E. Switch to an elemental formula.
3. A 4-month-old girl is brought to your office with worsening spitting up symptoms. You previously had seen her 2 weeks ago and diagnosed her with reflux. At that time, you recommended small frequent feeds, thickening feeds with rice cereal, burping, and upright positioning. Despite these measures, the mother reports that the infant is feeding less and is irritable after feeding. You notice that the child has not gained much weight since the last visit. Which of the following is the most appropriate next step in management?
   A. Erythromycin.
   B. Histamine-2 receptor antagonists.
   C. Metoclopramide.
   D. Nissen fundoplication.
   E. Switch to a lactose-free formula.
4. You are seeing a 6-year-old boy who has repeated asthma exacerbations. He is taking an inhaled corticosteroid daily as a controller medication and is slightly overweight. The mother reports that the boy has heartburn, chest discomfort, and occasional vomiting. In addition to referring him to a pulmonologist for asthma management, which of the following is the most appropriate immediate next step in management?
   A. Follow-up in the office in a couple of weeks.
   B. Food allergy testing.
   C. Increase his dose of inhaled corticosteroids.
   D. Order lung function tests.
   E. Prescribe acid reflux suppressants.

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5. A 14-month-old girl is brought to the office for follow-up. She has had reflux all her life and continues to be below the 5th percentile for weight. Proton pump inhibitors (PPIs) were tried which worked for a while but on tapering the medication, the symptoms return. The diagnosis of eosinophilic esophagitis is confirmed. Which of the following is the most appropriate next management step for this patient?
    - A. Four-food elimination diet consisting of milk, wheat, nuts, and shellfish.
    - B. Premedication with diphenhydramine prior to meals with no diet restriction.
    - C. Six-food elimination diet and swallowed topical corticosteroid combination regimen.
    - D. Six-food elimination diet consisting of milk, soy, eggs, wheat, nuts, and fish.
    - E. Two-food elimination diet consisting of animal milk and gluten-free cereals followed by a step up to 4- or 6-food elimination diet in nonresponders.

Common Substances of Abuse

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Education Gaps

1. With almost a third of adolescents admitting to ever drinking alcohol, and 25% ever using an illicit drug, substance abuse has a significant health impact on the adolescent population.
2. Pediatricians should be knowledgeable about the common substances abused by adolescents to properly prevent, recognize, counsel, and treat both acute and chronic use.

Objectives

After completing this article, readers should be able to:

1. Describe the general epidemiology of substance abuse in adolescents.
2. Determine when/how to evaluate and interpret substance abuse with laboratory testing.
3. Describe the pathophysiology, symptoms, and treatment for common substances of abuse.

Abstract

Adolescent substance abuse remains common, with almost a third of adolescents admitting to ethanol use, and a quarter admitting to illicit drug use. It is essential for pediatricians to regularly screen adolescent patients for substance use, because early initiation of drug use has been associated with physical, behavioral, and social health risks. Adolescents abuse what is common and readily available; this includes ethanol, over-the-counter products, marijuana, and inhalants. The most common and effective clinical treatments for significant toxicity from substances of abuse is symptomatic and supportive care including hemodynamic support, respiratory support, and sedation to control psychomotor agitation.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
CNS	central nervous system
GABA	γ-aminobutyric acid
GHB	γ-hydroxybutyrate
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
NMDA	N-methyl-D-aspartate
NSDUH	National Survey on Drug Use and Health
OTC	over-the-counter
SBIRT	Screening for Substance Use, Brief Intervention, and/or Referral to Treatment
THC	tetrahydrocannabinol

EPIDEMIOLOGY

The majority of adolescent substance abuse is initiated between 15 and 17 years of age, but can begin as early as age 10 years. (1) Initiation of substance abuse at an early age has been associated with long-term physical, behavioral, and social health risks including alcohol use and dependence, use of other substances (ie, marijuana, stimulants, and hallucinogens), school failure, high-risk sexual behaviors, and mental health disorders. (2)(3)(4)(5)(6)(7)(8)(9)(10)(11)(12) Poisonings and drug overdose is a leading cause of injury-related deaths in the adolescent population. (13) The death rate from drug overdose among adolescents aged 15 to 19 years more than doubled from 1999 (1.6 per 100,000) to 2007 (4.2 per 100,000). (14) Although there was a notable 26% decline from 2007 to 2014 (3.1 per 100,000), death rates from overdose increased in 2015 (3.7 per 100,000). In 2015, it was reported that most drug overdose deaths were unintentional, and rates were highest for opioids, specifically heroin. Early prevention, recognition, and intervention are critical in the adolescent age group.

Adolescents typically abuse what is inexpensive and readily available, such as alcohol, tobacco products, over-the-counter (OTC) pharmaceuticals, marijuana, and inhalants. Alcohol (ethanol) continues to be the most commonly abused substance. According to the 2015 National Survey on Drug Use and Health (NSDUH), 28.4% of youths aged 12 to 17 years ever drank alcohol and 5.8% reported binge drinking in the past month. (15) Twenty-five percent of adolescents admitted to ever using an illicit drug, and 8.8% used in the past month. The most common illicit drug was marijuana (12.6% in past year), followed by inhalants (9.1%) and hallucinogens (3.1%). A smaller number of adolescents admit to nonmedical use of prescription medications (2%). The Monitoring the Future survey reports that overall drug use, as well as alcohol and tobacco use, have slightly decreased since 2014. (16) However, hallucinogen abuse has remained steady, while abuse of cough and cold medication and novel drugs of abuse, such as synthetic stimulants and canthinones, has increased.

ROLE OF PRIMARY CARE CLINICIANS

The American Academy of Pediatrics (AAP) recommends an annual tobacco, alcohol, and drug use assessment beginning at the 11-year-old health supervision visit. (17) Research has demonstrated that many adolescents do not discuss substance abuse with their physicians because they are not asked, despite a desire to disclose. (18)(19)(20)(21) Emphasis should be placed on confidentiality, which will result in greater disclosure. When evaluating substance abuse, pediatricians should ask about nonmedical use of all categories of drugs: alcohol, nicotine, OTC and prescription medications, and illicit/recreational drugs (both common and novel). They should ask about frequency and routes of exposure (ingestion, injection, etc), which may reflect the magnitude of drug use. Primary care physicians should also inquire about caregiver knowledge of their drug use. This may reveal more information about the living and social environment that may need further investigation.

Several screening tools are available to help identify and stratify the risks of substance abuse. (22)(23)(24)(25)(26)(27) The AAP recommends the Screening for Substance Use, Brief Intervention, and/or Referral to Treatment (SBIRT) guidelines, which were designed by the US Substance Abuse and Mental Health Services Administration. In addition to SBIRT, the Society of Adolescent Health and Medicine has recommended several other tools that can be used to screen for various kinds of substance abuse focused at different age groups. Examples include the Alcohol Use Disorders Identification Test, Drug Abuse Screen Test screening tool, and the "Car, Relax, Alone, Forgotten, Family/friend, Trouble." (25) These screening tools have questions evaluating and qualifying risk factors associated with drug use: age at first use, frequency/pattern of use, and impact and consequences on physical, emotional, and social well-being. *The Diagnostic and Statistical Manual of Mental Disorders, 5th edition* describes a spectrum of abuse/dependence: experimentation, nonproblematic or problematic use, abuse, and dependence. (28)(29) All of these factors will help determine the degree of concern and amount of intervention that is needed: counseling and close follow-up in the primary care setting or referral to an addiction/drug rehabilitation specialist.

LABORATORY EVALUATION

Laboratory evaluation for substance abuse, such as urinary drug immunoassays, can provide ancillary information to a complete and thorough physical and mental health evaluation. Drug assays can help confirm, exclude, and/or specify systemic drug exposure. However, caution should be used when interpreting results. Standard urine drug screens have not been shown to change management in the emergency department or add any further information when obtaining a drug use history. (30)(31)(32) Obtaining a thorough confidential history and physician examination can provide great detail on acute and chronic substance use (Table 1).

Urine drug immunoassays are common qualitative tests for drug exposure. They are inexpensive, noninvasive, and

TABLE 1. **Substances of Abuse and Associated Clinical Symptoms**

	CLINICAL SYMPTOMS			
DRUG CATEGORY	**CARDIOVASCULAR**	**NERVOUS SYSTEM**	**GASTROINTESTINAL**	**OTHER**
Ethanol	Tachycardia or bradycardia, hypotension	Miosis, ataxia, agitation, sedation, coma	Pain, nausea, vomiting	Respiratory depression, hypoglycemia (young children)
Nicotine	Tachycardia and Hypertension (early), Bradycardia and Hypotension (late)	Seizures, sedation, coma, weakness/paralysis	Nausea, vomiting	
Marijuana	Tachycardia, hypertension	Agitation, sedation, psychosis	Pain, nausea, vomiting	
Antihistamines	Tachycardia, hypertension	Agitation, delirium, sedation, mydriasis, hallucinations	Decreased bowel sounds	Flushed, dry skin and mucous membranes, urinary retention, hyperthermia
Dextromethorphan	Tachycardia, hypertension, flushed	Agitation, delirium, sedation, mydriasis or miosis, ataxia, nystagmus, hyperreflexia, hallucinations		Hyperthermia
Inhalants	Tachycardia, dysrhythmia (rare)	Euphoria, sedation		Angioedema
Sedative hypnotics	Bradycardia, hypotension	Sedation, coma, ataxia, nystagmus		Respiratory depression
Hallucinogens	Tachycardia, hypertension	Euphoria, auditory and visual hallucinations, nystagmus, ataxia, psychosis, mydriasis, coma		Hyperthermia
Stimulants/ sympathomimetics	Tachycardia, hypertension	Agitation, psychosis, mydriasis	Nausea, vomiting, diarrhea	Hyperthermia, diaphoresis
Opioids/opiates	Bradycardia, hypotension	Euphoria, sedation, coma	Ileus	Respiratory depression

rapid. However, determination of exact timeline, route of exposure, and level of intoxication is difficult with urine immunoassays. Each category of drug has variable durations of detection after exposure, and has potential false-positive and -negative results (Table 2). (32)(33)(34) Common adulterants to avoid drug detection include addition of water (dilution), using another subject's urine sample, ingestion of diuretics or overconsumption of water (dilution), household chemicals, salt, and oxidants. (35)

Hair follicle testing is an additional noninvasive modality to detect drug exposure. Hair testing can evaluate for subacute or chronic exposure (typically weeks to 2–3 months earlier). However, it can be prone to external contamination and is dependent on an adequate hair sample (length) and proper sample preparation. Detection of drug metabolites can aid in distinguishing between a systemic exposure and external contamination. Like urine, hair testing is difficult to clinically correlate with the level of intoxication, exact timing, and route of exposure. The color of the subject's hair may also be a variable in the accuracy of results. (36)(37)(38)

Blood (whole, serum, plasma) testing is a more accurate modality for detecting systemic exposure and can make a better clinical correlation with the level of intoxication. However, this modality is invasive, often expensive, and generally can take several days to weeks for results, which limits its clinical usefulness for acute patient care.

Regardless of the sampling source, confirmatory testing should be considered when results of initial screening tests are unexpected, concerns for false-positive or -negative results exist, or specific compounds/drugs need to be identified. Biologic samples from the earliest time of symptom onset or suspected toxicity provide the best opportunity to clinically correlate intoxication and detect an exposure. The modality for confirmatory testing is typically either gas or high-performance liquid chromatography paired with mass spectroscopy. Results are quantitative rather than qualitative, and testing can be performed for specific

TABLE 2. **Common Drug Classes Found in Urine Drug Screening Immunoassays and Testing Characteristics**

URINE DRUG SCREENING CATEGORIES	DURATION OF DETECTION[a]	FALSE POSITIVES AND NEGATIVES[b]
Amphetamines	1-4 days	Can cross-react with decongestants, ADHD medications, Methamphetamines, MDMA, ephedrine, bupropion
Barbiturates	1-4 days	Phenobarbital can be detected for 3–4 weeks
Benzodiazepines	1-4 days	Can have false negatives for lorazepam, alprazolam, midazolam, and clonazepam. Diazepam can be detected for 3–4 weeks
Cocaine (benzoylecgonine)	2-4 days	Do not commonly occur
Opiates	1-4 days	False negatives can occur with synthetic and semi-synthetic opioids (oxycodone, hydromorphone, fentanyl, etc.)
Phencyclidine	1-8 days	Can cross-react with ketamine, dextromethorphan, diphenhydramine.
Marijuana (THC metabolites)	7-30 days	Reported false positives include dronabinol, efavirenz, proton pump inhibitors, nonsteroidal anti-inflammatory drugs

ADHD=attention-deficit/hyperactivity disorder; MDMA=3,4-methylenedioxymethamphetamine; THC=tetrahydrocannabinol.

[a] *Detection period varies and depends on chronicity of exposure.*

[b] *This is not an all-inclusive list of potential false positives/cross reactants and false negatives.*

substances rather than drug categories. The disadvantage of this modality is cost and significant delays in obtaining results.

COMMON SUBSTANCES OF ABUSE

Alcohol (Ethanol)

Over a quarter of adolescents admit to ever drinking alcohol, with almost 6% admitting to binge drinking in the past month. (15) Ingestion is the most common route of exposure for ethanol; however, there are reports of inhalation (vaporization) and exposure via other orifices (vaginal suppositories, rectal administration). (39)(40) Common household items may also contain high concentrations of ethanol including tinctures and essential oils, cosmetics, mouthwashes, rubbing alcohol, hand sanitizers, and cooking extracts (eg, vanilla). Ethanol is also limitedly available as a powder that can be reconstituted as a solution. (41)

Absorption of alcohol after ingestion is typically rapid and onset of intoxication is relatively quick in a naive user. (42)(43) Alcohol enhances the inhibitory effects of γ-aminobutyric acid (GABA) at the GABA-A receptor, while blocking the N-methyl-D-aspartate (NMDA) subtype of glutamate, an excitatory amino acid receptor. Intoxication can be more severe when coingested with other sedative-hypnotics. The potential blood ethanol concentration can be roughly estimated if a dose of ethanol is known. For a 60-kg patient (estimated total body water [60%] or volume of distribution $[V_d] = 36$ L) who ingested 4 “shots” of 40% ethanol solution, calculation is as follows:

$$1 \text{ shot} = 30 \text{ mL},\ 4 \text{ shots} = 120 \text{ mL}$$

$$120 \text{ mL} \times 40\% = 48 \text{ mL of } 100\% \text{ ethanol}$$

$$48 \text{ mL} \times 0.79 \text{ (specific gravity of ethanol)} \\ = 37.9 \text{ g or } 37{,}900\ \textit{mg of ethanol}$$

$$37{,}900 \text{ mg}/36 \text{ L} = 1{,}053 \text{ mg}/\text{L} = 105 \text{ mg}/\text{dL}$$

Many naive users can have signs of intoxication with blood concentrations as low as 20 to 60 mg/dL. The rate of metabolic degradation is constant, typically 20 mg/dL per hour. (42)(43) Severe complications occur after a significant ingestion or coingestion of other sedatives, and can lead to respiratory depression, vomiting with aspiration, or trauma. It is important to obtain a history again and repeat the physical examination after an intoxicated patient becomes sober (regardless of the ingestion or drug) to evaluate for trauma, coingestants, and other medical diagnoses. Urinary ethanol may detect exposure, but is prone to contamination and is difficult to clinically correlate. Breath ethanol detectors estimate blood ethanol concentration but is dependent on the exhalation effort of the subject, and can have a falsely elevated or low values because of many complicating factors.

(44) If accurate knowledge of ethanol exposure is needed, blood (serum) ethanol concentration is recommended.

Tobacco/Nicotine

Nicotine is derived from members of the genus *Nicotiana* plant. Exposure is commonly via inhaled (smoke, vaporized), oral (chew, gum, lozenges), and dermal (patches) routes. Initiation of tobacco use at a young age is concerning for the potential long-term health risks of chronic exposure: lung disease, cardiovascular complications, and cancers. In 2016, 20.2% of high school students admitted to using any tobacco product in the past 30 days. There have been recent declines in cigarette specific use trends. In 2016, 8 (8%) of 100 high school students reported smoking cigarettes in the past 30 days, a decrease from 15.8% in 2011. (15) In contrast, use of electronic cigarettes is increasing: in 2016, 11 (11.3%) of 100 high school students reported using electronic cigarettes in the past 30 days, increased from 1.5% in 2011. Although the long-term effects of inhaling vapor from electronic cigarettes are not known, it has been demonstrated to contain toxicants including heavy metals, formaldehyde, acetaldehyde, and acetone. (45)(46) The amount of nicotine absorbed through smoking is highly variable, depending on the product and the user. Cigars, pipes, and concentrated vaporization products typically have higher nicotine content than traditional cigarettes.

Nicotine binds to central nicotinic receptors and directly stimulates neurotransmitter release including dopamine, glutamine, norepinephrine, acetylcholine, GABA, serotonin, and endorphins. Low-dose exposures result in sympathomimetic agonism and symptoms include nausea/vomiting, tachycardia, hyperalert state, hypertension, and euphoria. With larger-dose exposures, parasympathetic and neuromuscular-blocking effects may be more prominent including central nervous system (CNS) depression, seizures, and paralysis. There is no specific treatment for nicotine toxicity besides symptomatic and supportive care. Confirmation of exposure can be sent for its metabolite, cotinine.

Marijuana/Cannabis

Marijuana is the illicit substance most abused by adolescents. (15) National surveys do not show any recent trends indicating increased abuse, but adolescent perception on risk of marijuana use to health continues to decline. (16) Marijuana contains several cannabinoids; tetrahydrocannabinol (THC) is the most psychoactive and responsible for most of the clinical effects. Most common routes of exposure are inhalation (smoke, vaporization) and ingestion (THC-infused food products). Onset of symptoms after inhalation is typically rapid with peak effects seen after only a few minutes. (47) Ingestion of marijuana can lead to delayed and prolonged effects, which can peak at 2 to 4 hours and last up to 8 hours. THC and other cannabinoids are agonists at the CB1 and CB2 receptor, which can be found in the central and peripheral nervous system and the immune system. Symptoms after marijuana use can be quite variable: sedation, ataxia, psychosis, anxiety, delirium, vomiting, and tachycardia. Highly concentrated inhaled products (waxes, dabs, budders) and edible products can contain high amounts of THC. These higher potency products can lead to more significant symptoms such as psychosis, anxiety, and agitation. (48)(49) Chronic marijuana use in adolescents has been associated with poor academic performance (including less likely to graduate high school), adulthood psychotic disorders and symptoms, and other illicit drug use and drug addiction. (50)(51)(52)(53)(54)(55)(56)(57)(58)(59)(60)(61)(62)

Short-acting benzodiazepines or antipsychotics can be helpful in controlling more severe behavioral and psychomotor symptoms. Cannabis hyperemesis syndrome is a clinical syndrome that has been described after chronic inhalational use. Symptoms include severe abdominal pain, vomiting, and nausea often relieved by hot bathing. (63)(64)(65)(66)(67)(68)(69)(70)(71) Standard treatment consists of intravenous fluid hydration, antiemetics, and benzodiazepines. Haloperidol and capsaicin cream has been shown to be most effective in case reports. (63)(64)(65)(66)(67)(68)(69)(70)(71)

Standard urine drug immunoassays are qualitative assays that detect THC metabolites, usually at the cutoff value of 50 ng/mL. They can be positive up to a week after acute use and several weeks after chronic use. Although contact "highs" can occur after passive smoke exposure, positive screening results after passive smoke exposure are rare and only reported in small, confined, and unventilated environments with large amounts of smoke. (72)(73)(74)(75)(76)(77) Synthetic cannabinoids, such as "k2" and "spice," have chemical structures different from THC. Thus, use of these products will not result in a positive THC/marijuana finding on a standard urine drug immunoassay.

OTC MEDICATIONS

OTC medications are often abused by adolescents because they are inexpensive and readily available. The most common class abused by adolescents includes ingredients of the cough-and-cold category of OTC medications. (78)(79)(80)(81)(82)(83)(84)(85)(86) Active ingredients include antihistamines (diphenhydramine, chlorpheniramine), cough suppressants (dextromethorphan), and decongestants (pseudoephedrine, phenylephrine). Antihistamines are also found in many OTC sleep aids and allergy medications.

Antihistamine ingestions typically lead to sedation but can result in antimuscarinic toxicity (dry mouth, blurred vision, photophobia, tachycardia, urinary retention, hyperthermia, mental confusion) by antagonism at the histamine (H1) receptors (Table 1). Rarely, diphenhydramine can have cardiotoxicity from blocking sodium channels, which results in QRS interval widening, and dysrhythmias. Deaths have been reported from significant overdoses. (87)(88)

Dextromethorphan is an isomer of a potent μ-agonist levorphanol. Common slang terms for dextromethorphan abuse includes "dexing, robo-tripping, triple Cs." Dextromethorphan agonism at opioid/μ receptors is weak but it is the mechanism for its therapeutic use as a cough suppressant. Dextromethorphan also has NMDA-receptor antagonism, which leads to the more common clinical sequelae in the setting of misuse and abuse. Physical examination findings of dextromethorphan intoxication include mydriasis or miosis, nystagmus, CNS depression, tachycardia, delirium/agitation, slurred speech, hyperreflexia, and visual hallucinations. (81)(85)(89)(90)(91)(92) Opioid toxidrome is not commonly encountered. Serotonergic effects, including altered mental status, hyperreflexia, and autonomic instability (hyperthermia, tachycardia, hypertension), can be seen in the setting of a large overdose or when ingested with other serotonergic xenobiotics. (93)

Pseudoephedrine and phenylephrine are both sympathomimetic and can lead to a hyperadrenergic state. Symptoms of sympathomimetic toxicity include agitation, hyperthermia, tachycardia, and hypertension. Typically, the amounts of these medications in OTC products are low and significant toxicity is rare.

Treatment for toxicity from any of these OTC cough and cold medication ingredients include control of psychomotor agitation, delirium, and seizures. Benzodiazepines, such as lorazepam, are first-line therapy. Physostigmine, an acetylcholinesterase inhibitor, can be considered to reverse antimuscarinic toxidrome from antihistamines. (94)(95)(96)(97)(98)(99)(100)(101)(102)(103) In a retrospective review, it was shown to be more effective in controlling agitation and reversing delirium than benzodiazepines. (102) However, reversal of antimuscarinic toxicity is short acting (15–45 minutes) and should not be used in patients with asthma, cardiotoxicity, or seizures. (103)(104) Physostigmine infusion has been used safely and effectively for patients with prolonged and persistent antimuscarinic effects. (105)(106) Sodium bicarbonate or acetate intravenous bolus infusions (1–2 mEq/kg) can be used to overcome sodium channel blockade in the setting of severe diphenhydramine cardiotoxicity. In the rare circumstance of hypertensive emergency resulting from sympathomimetics, direct vasodilators, including nitroprusside, and phentolamine can be beneficial. Acetaminophen is a common coingredient in OTC cough and cold products; patients should always be evaluated for potential toxicity by obtaining the acetaminophen concentration. (107)(108) Although not specifically detected on standard urine drug immunoassays, diphenhydramine commonly cross-reacts with the tricyclic antidepressant urine immunoassay, and both dextromethorphan and diphenhydramine cross-react with the phencyclidine immunoassay.

INHALANTS

Abuse of inhalants remains popular among adolescents and an estimated 9% of the US population 12 years and older have abused or misused an inhalant for psychoactive properties, more than any other age group. (15) Other terms for inhalation include "huffing," "bagging," and "dusting." Most inhalants are organic compounds containing hydrogen and carbon, or hydrocarbons. They are commonly used as solvents and diluents in many various household products including cleaners, aerosols, fuels, and essential oils. Hydrocarbons can be aliphatic or aromatic and may also contain halogens (bromide, fluoride, etc). Nitrous oxide is also abused as an inhalant and found as a propellant in products such as whipped cream.

After inhalation, onset of psychoactive effects is rapid. Hydrocarbons diffuse through the pulmonary system and readily cross the blood-brain barrier and affect neurotransmitters, which include glutamate/NMDA, GABA, dopamine, and opioid receptors. (109)(110) Symptoms can include CNS depression, euphoria, and tachycardia. Recreational use of inhalants has a short duration of effect. A rare complication is angioedema. (111) Chronic use of toluene can lead to renal tubular acidosis and resulting severe hypokalemia. (112)(113) It is postulated that hydrocarbons, specifically halogenated hydrocarbons, may sensitize the myocardium to catecholamines by inhibiting calcium signaling which may lead to cardiac dysrhythmias. (114) Chronic hydrocarbon inhalant abuse can lead to severe abnormalities of the nervous system, including neuropathies, neuropsychiatric disorders, encephalopathy, and dementia. (115)

Intoxication from acute inhalant abuse typically has rapid resolution of symptoms and medical treatment is often unnecessary. Prolonged hospital admission with potassium repletion may be necessary in the setting of renal tubular acidosis from toluene because of the significant weakness that may develop. Cardiac dysrhythmias should be treated with standard resuscitative measures. Catecholamines should be used cautiously because of the theoretical risk of worsening sensitized myocardium. Urine assays are available to detect urinary metabolites of specific hydrocarbons.

SEDATIVE-HYPNOTICS

Sedative-hypnotics include a diverse class of drugs and medications and are rarely abused by adolescents (estimated 23,000 or 0.1%). (15) Benzodiazepines are agonists at the GABA-A receptor and each individual benzodiazepine has varying time to onset and duration of action. Barbiturates are also agonists at the GABA-A receptor but may lead to more significant symptoms than benzodiazepines. γ-hydroxybutyrate (GHB) is an agonist at the GABA-B receptor and is medically used for narcolepsy to induce sleep. It is abused as a sedative and for body building (mechanism is a purported increase in deep sleep, resulting in increased growth hormones). GHB is known to cause a deep but short-lived coma. γ-butyrolactone and 1,4-butanediol are related to GHB and can lead to similar toxicity. Other sedative-hypnotics that are no longer commonly abused include chloral hydrate (when used with ethanol called "Mickey Finn"), methaqualone ("qualudes"), carisoprodol ("soma coma"), baclofen, and meprobamate.

Regardless of the sedative-hypnotic, common symptoms of abuse and overdose are CNS depression, nystagmus, and ataxia. Respiratory depression and hypotension can occur in large oral overdose, intravenous use, or coingestion with other sedative-hypnotics. Flumazenil is a benzodiazepine receptor antagonist that can be given to reverse the toxicity of benzodiazepine toxicity. However, flumazenil should be used sparingly because it can precipitate withdrawal and seizures with chronic use. (115)(116)(117) Life-threatening withdrawal from most sedative-hypnotics can occur with abrupt cessation after chronic use and can be associated with agitation, hallucinations, tachycardia, and seizures. Standard urine drug immunoassays for benzodiazepines can be misleading, because they test for the common metabolite of select benzodiazepines: diazepam, chlordiazepoxide, clorazepate, and temazepam. These metabolites do not occur in the metabolism of commonly used benzodiazepines, including lorazepam, clonazepam, midazolam, and alprazolam, and result in false negatives.

HALLUCINOGENS

Hallucinogens are a diverse group of substances that alter and distort perception, thought processes, and mood. In 2016, the NSDUH reported that 1.4 million Americans older than 12 years were current users of hallucinogens (15). Several hallucinogens are commonly abused. The synthetic lysergamide, LSD, is derived from an ergot alkaloid of the fungus, *Claviceps purpurea,* and is a water-soluble, colorless, tasteless, and odorless powder. Mescaline is a naturally occurring hallucinogen found in peyote (*Lophophora williamsii*), a small blue-green spineless cactus found throughout the southwestern United States and northern Mexico. Peyote buttons are the round, fleshy tops of the cactus that can be removed, dried, and eaten. Six to twelve peyote buttons, or 270 to 540 mg of mescaline, are routinely required to produce hallucinogenic effects. (118) The onset of hallucinations begins 1 to 3 hours after ingestion and can last for up to 12 hours. (119) *Psilocybe* mushrooms contain the hallucinogen psilocybin. Ingestion of at least 5 g of psilocybin-containing mushrooms may be required to produce hallucinogenic effects, which are typically shorter in duration (4 hours). (120) *Salvia divinorum* is an herb and its use results in vivid hallucinations and synesthesia as well as diuresis, nausea, and dysphoria. (121) Recreational nutmeg use results in euphoria and hallucinations as well as nausea, vomiting, dizziness, flushing, tachycardia, and hypotension.

Physiologic abnormalities typically precede the perceptual changes and hallucinations (auditory and visual) induced by lysergamides. Sympathomimetic effects are common and dysphoria may compel patients to react to stimuli with unpredictable and aggressive behaviors. (122) Potentially life-threatening complications, such as hyperthermia, coma, respiratory arrest, hypertension, tachycardia, and coagulopathy, were described in 8 patients with a massive LSD overdose. (123) Serotonin toxicity could theoretically occur after the use of hallucinogens or with the use of other serotonergic medications such as serotonin-reuptake inhibitors. (124)(125) The vast majority of morbidity from hallucinogen use stems from secondary trauma that patients sustain while intoxicated and unaware of their surroundings.

Most hallucinogen users rarely seek medical attention because they experience only the desired effect of the drug and rarely produce life-threatening toxicity. There should be minimal external stimulation to prevent further agitation, and benzodiazepines can be used to treat psychomotor agitation. Morbidity and mortality can occur secondary to hyperthermia, rhabdomyolysis, hepatic necrosis, and disseminated intravascular coagulopathy. Physical restraint (without chemical restraint) should be avoided to prevent hyperthermia and rhabdomyolysis. Treatment of serotonin toxicity is largely supportive and requires avoidance of further exposure to serotonergic substances and medications. Specific therapy with agents like cyproheptadine has been used. (126) Long-term consequences of chronic LSD use include prolonged psychotic reactions, severe depression, exacerbation of preexisting psychiatric illness, and hallucinogen persisting perception disorder. (127)

While hallucinogens such as LSD can be detected on urine immunoassay, confirmation using high-performance liquid chromatography or gas chromatography is necessary for most other hallucinogens. False-positive results on urine immunoassay for LSD are reported after exposure to several medications, including fentanyl, sertraline, haloperidol, or verapamil. (128)(129)

STIMULANTS/SYMPATHOMIMETICS

According to NSDUH, about 92,000 (0.4%) adolescents aged 12 to 17 years of age were current misusers of stimulants. (15) Stimulants include various substances including amphetamines (OTC, prescription, illicit), 3,4-methylenedioxymethamphetamine (MDMA), methylxanthines, and cocaine.

Amphetamines (Including Methamphetamines, MDMA)

Amphetamines represent a group of compounds with a common structure known as phenylethylamines. The pharmacologic effects of amphetamines are diverse, with their primary mechanism of action being the release of catecholamines, particularly dopamine, norepinephrine, and serotonin from presynaptic terminals and resulting in a hyperadrenergic state. Sympathomimetic effects are the most prominent clinical sequelae. (130)(131)(132) Life-threatening complications include intracerebral hemorrhage, stroke, seizures, myocardial infarction, ischemic colitis, obstetric complications, and dysrhythmias. (129)(130)(131)(132)(133) Without rapidly reversing the systemic signs and symptoms, multisystem organ failure and death may occur.

Evaluation of core body temperature is essential to diagnose the presence and degree of hyperthermia, which is a frequent and rapidly fatal manifestation in patients after significant amphetamine exposure. (134) Significant hyperthermia requires immediate and aggressive interventions to achieve rapid cooling. (135)(136)(137)(138) Benzodiazepines are effective for the treatment of psychomotor agitation induced by acute amphetamine overdose, and sedation should be titrated rapidly until the patient is calm. Physical restraints should be removed as soon as possible to prevent rhabdomyolysis and further heat generation. For seizures, benzodiazepines are also first-line therapy, followed by barbiturates or propofol. Dopamine antagonists such as haloperidol, droperidol, and olanzapine are options for amphetamine-induced delirium.

Qualitative urine immunoassays are available for amphetamines; however, false-positive and negative results are common (Table 2). Confirmatory testing is recommended to identify specific amphetamine compounds. Even with confirmatory testing, misidentification of isomeric substances such as L-methamphetamine (decongestant) with d-methamphetamine (illicit drug) can occur. (139)

3,4-Methylenedioxymethamphetamine

MDMA is also known as “ecstasy,” “E,” “Adam,” “XTC,” “molly,” and “MDM.” (137)(138)(139) Analogs exist that produce similar clinical effects, including 3,4-methylenedioxy-N-ethyamphetamine (MDEA or “Eve”), 3,4-methylenedioxyamphetamine (MDA or “love drug”), and paramethoxyamphetamine. MDMA is available in a range of doses (50–200 mg) in colorful and branded tablets and has a higher affinity for serotonin transporters (~10 times greater) than for dopamine and norepinephrine transporters. MDMA and similar analogs are so-called “entactogens” and are capable of producing euphoria, inner peace, and a desire to socialize. (140)(141)(142)(143)(144) People who use MDMA report that it enhances pleasure, heightens sexuality, and expands consciousness without the loss of control. Negative effects reported with acute use included ataxia, restlessness, confusion, poor concentration, and impaired memory. Significant free water intake combined with sodium loss from physical exertion in dance clubs may exacerbate the development of hyponatremia and cerebral edema. The use of “Molly” as well as “Molly” overdose has been associated with intracranial hemorrhage. (145 Chronic MDMA use has been associated with sleep and behavioral health disturbances, impulsiveness, and memory deficits). (146)

Methylxanthines (Caffeine, Theophylline, Theobromine)

Caffeine is the most assessable methylxanthine found in many beverages and in powdered form. Methylxanthines cause the release of endogenous catecholamines with stimulation of β 1 and β 2 receptors and act pharmacologically as adenosine receptor antagonists. (147) Adenosine antagonism leads to the release of norepinephrine and epinephrine. Methylxanthines also inhibit phosphodiesterase, the enzyme responsible for degradation of intracellular cyclic AMP, which has many effects, including an increase in intracellular calcium concentrations.

In adults, caffeine doses of 50 to 200 mg result in increased alertness, decreased drowsiness, and lessened fatigue, and caffeine doses of 200 to 500 mg produce adverse effects such as tremor, anxiety, diaphoresis, and palpitations. Most significant acute overdoses result in severe, protracted emesis, palpitations, tachycardia, and chest pain. Although sinus tachycardia is the most common finding, tachydysrhythmias including supraventricular tachycardia, multifocal atrial tachycardia, atrial fibrillation, premature ventricular contractions, and ventricular tachycardia have been reported. (148) Clinically significant dysrhythmias occur in 35% of patients with chronic theophylline poisoning but in only 10% of acute poisoning cases. (149) Ventricular dysrhythmias may occur at serum concentrations of 40 to 80 μg/mL in patients with chronic theophylline overdoses and at serum concentrations greater than 80 μg/mL in patients with acute overdoses. Complications of vasoconstriction may occur including myocardial ischemia/infarction and cerebral vasoconstriction/stroke. (150)(151)(152) Caffeine promotes and prolongs seizures as adenosine antagonism lowers the seizure threshold. (153)(154) Skeletal muscle excitation, which may include tremor, fasciculation, hypertonicity, myoclonus, or even rhabdomyolysis, can occur. (155)(156)(157)(158) Severe hypokalemia, hypomagnesemia, and hypophosphatemia may also result, similar to toxicity from other β-agonists. (159)(160)(161)(162)

Electrocardiography and serum electrolyte measurement are recommended in the evaluation for methylxanthine toxicity. Multiple-dose activated charcoal is effective in enhancing the elimination of caffeine but may be difficult to administer due to nausea. Otherwise supportive care including antiemetics, electrolyte repletion (hypokalemia), and fluid resuscitation is recommended. α-adrenergic agonists (phenylephrine or norepinephrine) are effective vasopressors. In rare cases of refractory hypotension, the administration of an adrenergic antagonist may reverse $\beta 2$ adrenergic–mediated vasodilation. Propranolol, esmolol, and metoprolol have been used successfully to treat methylxanthine-induced hypotension. (163)(164) Because of the antagonist effects at the adenosine receptor, administration of adenosine may not convert a methylxanthine-induced supraventricular tachycardia. Benzodiazepines may help in both CNS and cardiovascular effects by abating CNS stimulation and releasing catecholamines. Seizures not controlled with 1 or 2 therapeutic doses of a benzodiazepine should be treated with a barbiturate or propofol. Charcoal hemoperfusion was once considered the most effective method of enhanced elimination of methylxanthines, decreasing the half-life to 2 hours and increasing its clearance up to 6-fold. (165)(166)(167)(168) However, with the relative unavailability of this modality, hemodialysis is an excellent therapy. (169) Indications for hemodialysis therapy include clinically significant exposure with a serum theophylline or caffeine concentration greater than 90 μg/mL and symptoms, regardless of clinical stability and chronic theophylline poisoning associated with a serum theophylline concentration above 40 to 60 μg/mL or with a deteriorating clinical status.

Cocaine

Cocaine is contained in the leaves of *Erythroxylum coca*, a shrub found in Colombia, Peru, Bolivia, the West Indies, and Indonesia. Cocaine can be ingested, inhaled, insufflated, or injected. Cocaine increases excitatory amino acid concentrations in the brain by blocking the reuptake of biogenic amines such as serotonin, dopamine, norepinephrine, and epinephrine. Cocaine can affect multiple organ systems, mostly with its effects on the cardiovasculature system. Similar to other local anesthetics, cocaine blocks neuronal and cardiac sodium channels, which can lead to ventricular dysrhythmias and seizures. (170)(171)(172)(173)(174) Furthermore, cocaine blocks cardiac potassium channels, resulting in QT prolongation and potentially torsade de pointes. (173) Cocaine can predispose users to vascular occlusions by activating platelets and causes α-granule release, resulting in platelet aggregation. (175) Experiments in human volunteers demonstrate that smoking cocaine causes bronchospasm. (176)

As in the case of all poisoned patients, the initial emphasis must be on stabilization, based on the patient's symptoms, including fluid resuscitation, vasopressors, and respiratory support. If tracheal intubation is required, the use of succinylcholine is contraindicated because of potential rhabdomyolysis and hyperkalemia. In addition, plasma cholinesterase metabolizes both cocaine and succinylcholine and their simultaneous use could either prolong cocaine toxicity or lead to paralysis. (177) For severe cocaine toxicity, hyperthermia is the most critical vital sign abnormality and rapid cooling measures are paramount. A meta-analysis evaluating benzodiazepines and antipsychotics in animal models of cocaine toxicity found that both reduced mortality. However, benzodiazepine treatment reduced mortality by 52% compared with only 29% reduction in mortality with antipsychotics. (178) The use of a β-adrenergic antagonist is contraindicated because of the concern for the theoretical development of unopposed α-adrenergic stimulation. Any organ dysfunction caused by vasospasm not resolved with sedation, cooling, and volume resuscitation could be treated with vasodilators such as phentolamine. An acute coronary syndrome should be treated with standard measures. Although cocaine is rapidly metabolized, standard urine drug immunoassays readily detect the metabolite of cocaine, benzoylecgonine, which remains detectable in the urine for 2 to 3 days after the last use. (179) Long-term effects of chronic cocaine use include malnourishment, stroke, seizures, and movement and psychiatric disorders. (180)

OPIOIDS/OPIATES

The adolescent population is no exception when it comes to the opioid misuse and abuse epidemic. In 2016, almost 900,000 adolescents (3.6%) reported misusing opioids in the past year. (15) The number increases to over 2 million between ages 18 and 25 years. Opioids are alkaloids naturally derived directly from the opium poppy plant. These include morphine, codeine, thebaine, and noscapine. Opioids are a broader class of substances capable of binding to opioid receptors. Semisynthetic opioids, such as heroin and oxycodone, are created by chemical modification of an opiate. A synthetic opioid is a chemical that is not derived from an opiate, and is capable of binding to an opioid receptor and producing opioid effects clinically. Depending on the opioid or opiate, onset of action and duration action can be quite variable.

Patients poisoned by opioids predictably display features of the opioid syndrome: mental status depression, hypoventilation, miosis, and hypoperistalsis. Opioid agonists cause hypoventilation by reducing the sensitivity of the medullary chemoreceptors to hypercapnia and depressing the ventilatory response to hypoxia. (181)(182) The combined loss of hypercarbic and hypoxic drive eliminates the stimulus to breathe; respiratory depression is the primary cause of death after overdose. Arteriolar and venous dilation secondary to opioid use may result in a mild reduction in blood pressure. True opioid-induced hypotension appears to be mediated by histamine release. Methadone may interfere with normal cardiac repolarization and produce QT interval prolongation with a predisposition to the development of torsade de pointes. (183)(184) Seizures should be anticipated in patients with meperidine, propoxyphene, tapentadol, or tramadol toxicity. Abrupt cessation after habitual use can induce withdrawal symptoms, which can include anxiety, irritability, diaphoresis, vomiting, and tremor. Although this withdrawal symptom has significant discomfort, as opposed to many sedative-hypnotics, it is not life-threatening.

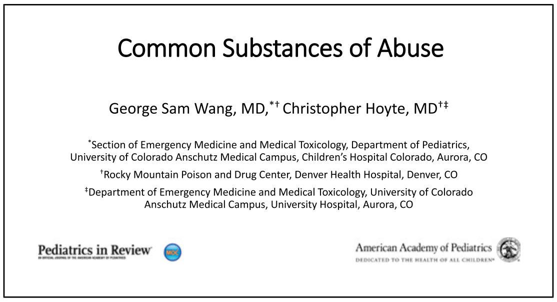
Treatment of opioid/opiate toxicity is to ensure adequate hemodynamics and respiratory drive. Naloxone can be administered through various routes, including intravenous, intramuscular, intranasal, and subcutaneous. Standard intravenous dosing is 0.01 mg/kg, followed by 0.1 mg/kg if the response is not achieved. Naloxone infusion has been used when long-acting opioid/opiate has been ingested and respiratory depression events continue to occur. Patients should be monitored for a minimum of 3 to 4 hours after initial naloxone dosing for short-acting opioid/opiate (heroin) intoxication, though shorter times have occurred without significant complications. (185)(186) Longer observation times are warranted with longer-acting opioid analgesics. Alternative to naloxone administration is intubation and mechanical ventilation.

Standard urine immunoassays detect opiates by identifying a common metabolite to codeine, heroin, and morphine. Other semisynthetic and synthetic opioids are not routinely detected and will result in a negative opiate screening result. Confirmatory testing is recommended if a specific opioid/opiate needs to be identified.

Summary

- Substance abuse is common in adolescents, with almost 30% admitting to ever using alcohol and 25% ever trying an illicit drug.
- Most adolescents will abuse substances that are inexpensive and easily available including alcohol, nicotine products, over-the-counter medications, marijuana, and inhalants.
- Readily available urinary drug immunoassays may detect some categories of substance abuse. However, both false-positive and false-negative results commonly occur for many substances and may not clinically correlate with acute intoxication.
- It is important for primary care physicians to be knowledgeable about substances of abuse, and privately screen for use and abuse during age-appropriate physical examinations.
- Based primarily on expert consensus and clinical experience, symptomatic and supportive care is often sufficient for the clinical treatment of most intoxications. This includes hemodynamic support (intravenous fluids, vasopressors), airway management, and sedation for significant psychomotor agitation, psychosis, and delirium. However, more resources are necessary for the evaluation and treatment of associated substance use and behavioral health disorders and the secondary impact on caregivers and family.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/8/403.supplemental.



Common Substances of Abuse

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1. A local district school health advisory council is implementing a drug education program for middle-school students. The program will focus on education by school nurses about the various substances of abuse and their dangers. While the program's discussion should cover all substances, based on reported abuse rates in junior high school, dangers surrounding the abuse of which of the following substances should be particularly emphasized by this program in this student population?
   - A. Alcohol.
   - B. Hallucinogens.
   - C. Inhalants.
   - D. Marijuana.
   - E. Prescription medications.
2. An 11-year-old boy is brought to the clinic for his health supervision visit. He is healthy, has had no recent illnesses, and is not taking any medications. His parents report that he is a "good kid" who does well academically, but they worry about him being exposed to drugs and influenced by his peers at school. The clinician explains to the parents that their son is entering the age whereby part of the interview in the visit is done alone with the patient while the parents sit in the waiting room as the clinician conducts a psychosocial assessment. Based on the American Academy of Pediatrics recommendation, an annual tobacco, alcohol, and drug use assessment should be conducted beginning at the 11-year-old well visit. Which of the following is the preferred method for completing this screening for tobacco, alcohol, and drug use in this patient?
   - A. Hair follicle analysis.
   - B. High-performance liquid chromatography.
   - C. Serum drug levels.
   - D. Substance use, brief intervention, and/or referral to treatment guidelines.
   - E. Urinary drug immunoassay.
3. A 16-year-old boy is brought into a school-based health clinic by his friends. He appears agitated and reports poor sleep over the past week. Vital signs show an increased heart rate, hypertension, and increased temperature. He is oriented to time, person, and place and exhibits no psychotic features. Abuse of which of the following substances is most likely responsible for this clinical presentation in this patient?
   - A. Alcohol.
   - B. Inhalants.
   - C. Hallucinogens.
   - D. Opioids.
   - E. Stimulants.
4. A 17-year-old boy was brought to the emergency department by his roommate because of altered mental status. The roommate was away for the weekend and returned on Sunday night to find the patient lying on the couch, incoherent, and having unsteady gait. In the emergency department, the patient was noted to be sleepy with altered mental status, nystagmus, and ataxia. Which of the following substances of abuse is most likely responsible for the clinical presentation of this patient?
   - A. Antihistamines.
   - B. Ethanol.
   - C. Inhalants.
   - D. Sedative hypnotics.
   - E. Stimulants.

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5. A 16-year-old female gymnast was sent from class to the school health room because she was "sleepy in class." The patient had back surgery for spondylolisthesis 6 weeks ago and restarted gymnastic training earlier this week. In the health room, she was noted to be sleepy, with shallow breathing and a low respiratory rate. 911 was called. The Emergency Medical Technicians (EMTs) assessed the patient to have depressed mental status, decreased respiratory rate, symmetric pinpoint pupils, and decreased bowel sounds. Pulse oximetry finding was 94% on room air. The patient was transported to the emergency department. The EMTs notified their supervising physician of the transport. Initial administration of which of the following en route is most likely to be recommended by the supervising physician?

   A. Benzodiazepines.
   B. Methadone.
   C. Naloxone.
   D. Oxygen.
   E. Sympathomimetics.

Index of Suspicion

1 Hemoptysis in a Healthy 13-year-old Boy

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Winningham and Estrellado-Cruz have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 13-year-old boy presents with cough and hemoptysis of 1 week duration. His cough is nonproductive and he describes a small amount of hemoptysis every day. There is no history of fever, changes in appetite, weight loss, exercise intolerance, orthopnea, or chest pain. His mother does report that he has had occasional night sweats.

Vital signs at the time of hospital admission are as follows: temperature, 100.8°F (38.2°C); heart rate, 100 beats/min; blood pressure, 109/55 mm Hg; respiratory rate, 22 breaths/min; and oxygen saturation, 98% on room air. His weight is 76 lb (34.4 kg) (<1st percentile). Physical examination findings are normal.

Laboratory studies include the following: white blood cell count, 7,400/μL (7.40×10^9/L); hemoglobin level, 7.9 g/dL (79 g/L); red blood cell count, $7.04\times10^3/\mu$L; mean corpuscular volume, 79.7 μm^3 (79.7 fL); reticulocyte count, 1.7% (0.017); platelet count, $420\times10^3/\mu$L (420×10^9/L); and elevated inflammatory markers, with an erythrocyte sedimentation rate of 92 mm/hour and a C-reactive protein level of 4.9 mg/dL (49 mgL). His serum electrolyte levels and liver function test results are normal.

His initial chest radiograph shows consolidation in the right upper lobe. Due to concern for tuberculosis (TB), quadruple anti-TB medications (rifampim, ethambutol, isoniazid, and pyrazinamide) are started on admission. Additional evaluation includes QuantiFERON-TB Gold (Qiagen, Hilden, Germany), sputum acid-fast bacillus stain and culture, aerobic respiratory culture, human immunodeficiency virus antibody screen, and histoplasma antibody and mycoplasma immunoglobulin (Ig) M and IgG antibody levels. Results of these tests are normal. Further imaging and subsequent laboratory testing lead to the diagnosis.

DISCUSSION

The differential diagnosis included an infectious process such as TB, infections with other mycobacterium, histoplasma, or mycoplasma versus an intrinsic lung injury such as a vasculitis, pulmonary hemosiderosis, or sarcoidosis. On hospital admission, a chest radiograph was performed that showed left upper lobe and right lower lobe lesions. The patient continued to have hemoptysis, and with the abnormal chest radiograph findings, a chest computed tomographic scan was performed. Findings revealed mixed nodular and ground glass consolidation (Fig 1). Bronchoalveolar lavage was subsequently performed that revealed greater than 80% hemosiderin-laden macrophages. A complete rheumatologic evaluation revealed elevated antimyeloperoxidase (MPO) antibody level greater than 8.0 (normal is <0.4) and an indeterminate perinuclear antineutrophil cytoplasmic antibody (p-ANCA). Lung biopsy showed mild capillaritis (ie, inflammation of the capillary vessels) (Fig 2), and renal biopsy revealed proliferative glomerulonephritis with crescent formation (Fig 3). Clinicians concluded that his condition was most consistent with microscopic polyangiitis (MPA) based on a positive anti-MPO antibody, which strongly suggests ANCA-related vasculitis along with tissue biopsy findings. His anti-TB medications were eventually discontinued given a negative TB evaluation.

The Condition

The ANCA-associated vasculitides (AAV) are infrequent diagnoses in childhood. Microscopic polyangiitis is a systemic small-vessel vasculitis that is primarily manifested with findings of necrotizing glomerulonephritis and pulmonary capillaritis. The AAV are autoimmune diseases targeting either proteinase 3 or MPO. The incidence is approximately 1:100,000 in the general population. Males are more frequently affected than females, and the average age at onset is approximately 50 years. In children, the condition is rare and usually manifests at the beginning of the second decade of life.

Clinical Presentation

The main organs involved in AAV include the kidneys, lungs, joints, heart, peripheral nerves, skin, and central nervous system, clinically manifesting as myalgias, arthralgias, arthritis, purpura, abdominal pain, gastrointestinal tract bleeding, and peripheral neuropathy.

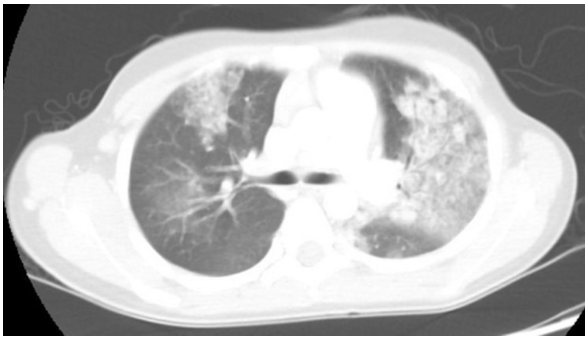

Figure 1. A chest computed tomographic scan shows mixed nodular and ground glass consolidations in both lungs.

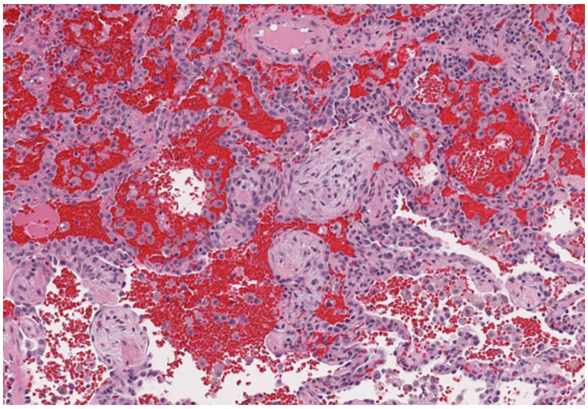

Figure 2. Lung biopsy shows evidence of mild capillaritis.

Pulmonary and renal complications are common in AAV. Renal involvement is characterized by a rapidly progressive glomerulonephritis. The most common manifestation of lung involvement in the anti-AAV is alveolar hemorrhage, which has a similar frequency of occurrence in children and adults. The pulmonary capillaritis is the direct cause of the manifestation of alveolar hemorrhage.

Lung involvement is an important contributory factor to morbidity and mortality. The diagnosis should be suspected in patients with hemoptysis, anemia, and diffuse alveolar infiltrates on chest radiography. Patients can present with chronic findings of isolated anemia, persistent cough, dyspnea on exertion, and recurrent radiologic infiltrates.

Etiology

Diffuse alveolar hemorrhage (DAH) syndromes occur as a result of injury to the small vessels in the pulmonary circulation; DAH is classified into 2 groups: 1) absence of pulmonary capillaritis or 2) presence of pulmonary capillaritis

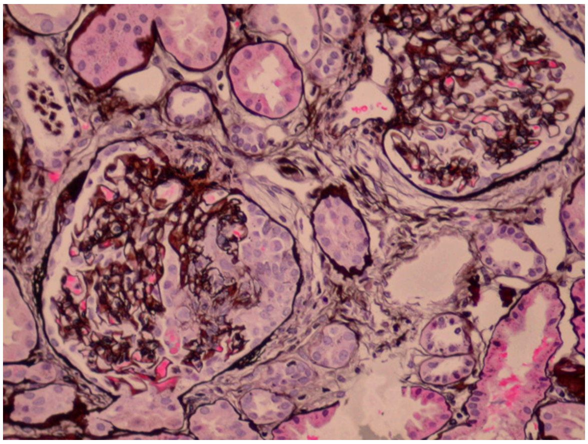

Figure 3. Renal biopsy shows proliferative glomerulonephritis with crescent formation.

(characterized by inflammatory disruption of alveolar interstitium).

Without capillaritis, DAH can be caused by cardiac disease (mitral stenosis, pulmonary veno-occlusive disease, arteriovenous malformation, pulmonary hypertension, pulmonary hemangiomatosis) and noncardiac pathology (idiopathic pulmonary hemosiderosis, bone marrow transplant, coagulation disorders, celiac disease, infanticide).

With pulmonary capillaritis, DAH is most commonly caused by autoimmune disorders, including Wegener granulomatosis, Goodpasture syndrome, MPA, systemic lupus erythematosus, antiphospholipid antibody syndrome, Henoch-Schonlein purpura, IgA nephropathy, polyarteritis nodosa, and drug-induced capillaritis.

Pathophysiology in MPA is based on autoantibodies, produced by B lymphocytes and plasma cells, activating a proinflammatory phenotype of neutrophils that cause necrotizing damage to vascular walls of small vessels, often involving the kidneys and lungs. The activated neutrophils release reactive oxygen species and lytic enzymes that damage and lyse endothelial cells. There may be an association of increased levels of autoantibodies preceding the onset of clinical relapse of AAV.

Diagnosis

A computed tomographic scan is recommended to confirm the diagnostic findings identified on chest radiography. Helpful markers in making the diagnosis of MPA are the presence of the p-ANCA and the MPO antibody. The ANCAs are found in most patients with MPA, and most of these are p-ANCA. Although ANCA is a valuable diagnostic tool, it is limited in monitoring disease activity and in predicting response to therapy. To look for evidence of vasculitis, it is often recommended to perform a biopsy of the involved tissue.

Management

When immunosuppression treatment such as cyclophosphamide (CYC) and high-dose glucocorticoids were introduced as management for AAV, 1-year mortality was reduced from 80% to 10% to 20%. However, malignancy and infertility are adverse effects of CYC. In terms of safety, rituximab (RTX) seems more favorable than CYC. In addition, studies have shown that in patients with AAV who have renal involvement, RTX and CYC yield identical remission rates. As a chimeric monoclonal antibody, RTX interrupts this antibody-mediated autoimmune disease by depleting precursors of ANCA-producing cells.

Because AAV are autoimmune, other organs should be evaluated and monitored for their function.

Patient Course

He was started on management with pulse corticosteroids and RTX, which resulted in a good clinical response, his renal function was stabilized, and inflammatory markers of p-ANCA and MPO titers improved. He had 1 pulmonary function test performed 2 months after discharge from the hospital that revealed normal spirometry and total lung capacity.

Pulmonary function test results have remained stable. He is continuing with maintenance therapy with RTX infusion for a total of 18 months, as well as prophylactic trimethoprim-sulfamethoxazole.

Lessons for the Clinician

- Microscopic polyangiitis is a rare disease in children, and without aggressive therapy it has a poor prognosis.
- The diagnosis should be suspected in patients with hemoptysis, anemia, and chest radiographic findings that reveal a diffuse alveolar infiltrate pattern.
- Patients can present with chronic findings of isolated anemia, persistent cough, dyspnea on exertion, and recurrent radiologic infiltrates.
- The relapse and mortality rates are reduced with cyclophosphamide and high-dose glucocorticoids.
- As an approved alternative for remission induction and because of its favorable adverse effect profile, rituximab is used more frequently to treat patients with relapsing or refractory disease.

ACKNOWLEDGMENT

The authors acknowledge the Children's Mercy Hospital Pathology Department for lung biopsy and renal biopsy slide.

Note. This case is based on a presentation by Drs Winningham and Estrellado-Cruz at the CHEST Conference: Montréal, Québec, Poster Session: Pulmonary Manifestations of Systemic Disease Student/Resident Case Report Posters I, Presentation Date: October 27, 2015, Poster Number: 3873.

An Abstract of this case is also published in the CHEST Journal as Microscopic Polyangiitis, a rare Pediatric Case. Estrellado W et al. CHEST, Volume 148, Issue 4, 877A.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/39/8/415.

Index of Suspicion

2 Hemolacria, Hematochezia, and Hematuria in an 11-month-old Boy

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PRESENTATION

A previously healthy 11-month-old boy born at full-term presents with a rash for 3 days. It began as a single purpuric lesion on his right ear and progressed over 2 days to involve his face (Fig 1) and all extremities. On the day of presentation, mom reports swelling of his face, hands, and feet; nasal congestion; cough; bilateral conjunctivitis; and "red tears." He has poor oral intake and urine output, worsening fussiness, is difficult to console, but has no tactile fever. Two weeks ago he completed 10 days of amoxicillin for acute otitis media. His medical, surgical, travel, allergic, and family histories are otherwise unremarkable. His vaccines are up to date. He takes no prescribed or over-the-counter medications.

On physical examination he is crying and appears uncomfortable. He is afebrile, and tachycardic to 158 beats/min with normal blood pressure and respiratory rate. He has innumerable 1- to 4-cm, violaceous, erythematous, nonblanching, and nonpruritic targetoid patches and plaques on his face and extremities (Figs 1–3), sparing his abdomen, palms, soles, back, and genitals. He has rhinorrhea, bilateral conjunctivitis, red-stained tears (hemolacria), erythematous tympanic membranes, and a targetoid patch on the hard palate. He has painful, nonpitting edema of his face, hands, feet, and scrotum, with intact cremasteric reflexes bilaterally. The remainder of his examination findings are normal.

The white blood cell count is normal, complete metabolic panel shows evidence of dehydration, urinalysis is significant for hematuria, and stool is occult blood positive. An oropharyngeal swab is positive for enterovirus/rhinovirus.

AUTHOR DISCLOSURE Drs Manzano, Shantharam, Webb, Finelt, and Hengel have disclosed no financial relationships relevant to this article. Dr Manzano's current affiliation is Massachusetts General Hospital, Boston, MA. Dr Webb's current affiliation is Community Health Services, Hartford, CT. Dr Hengel's current affilaition is Maimonides Children's Hospital, Brooklyn, NY. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

Hospital Course

The child was admitted to the inpatient unit for management of dehydration and further evaluation of the described rash. He became febrile during the admission and continued to have hemolacria, occult hematuria, and hematochezia for several days. Hemolacria was observed with and without conjunctivitis. On admission, scrotal edema was observed, and scrotal ultrasonography showed

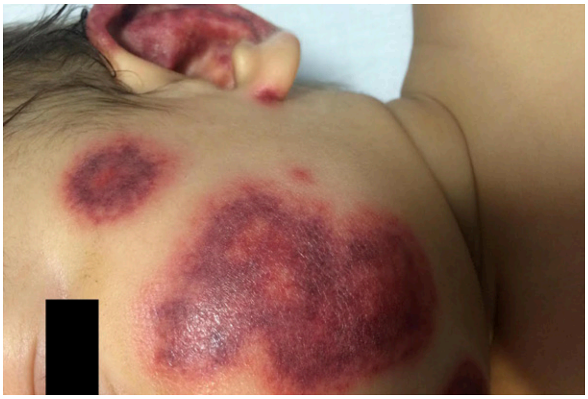
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Figure 1. Characteristic targetoid lesions present on the patient's left ear and face.

adequate blood flow and bilateral orchitis and epididymitis. There was low suspicion for significant renal disease given his normal levels of urine protein, creatinine, and urine output once rehydrated.

A dermatology consult was sought, and the patient was diagnosed as having acute hemorrhagic edema of infancy with extensive mucosal involvement. Supportive inpatient care was provided. He was discharged several days after admission after improvement of oral intake. The patient's rash and edema remained but were improving on discharge.

The Condition

Vasculitides are among the many etiologies responsible for the development of a rash in the pediatric population. Our patient presented with acute hemorrhagic edema of infancy (AHEI), a benign leukocytoclastic vasculitis that manifests with a dramatic rash despite a self-limited and benign course. The exact etiology of AHEI is unknown; it is loosely associated with an infectious trigger and certain medications and immunizations. Upper respiratory tract infections or gastroenteritis, aspirin, acetaminophen, penicillin, erythromycin, cephalexin, over-the-counter cough syrup, and the diphtheria-pertussis-tetanus, conjugated *Haemophilus influenzae,* and measles-mumps-rubella vaccines are all roughly correlated with onset of AHEI.

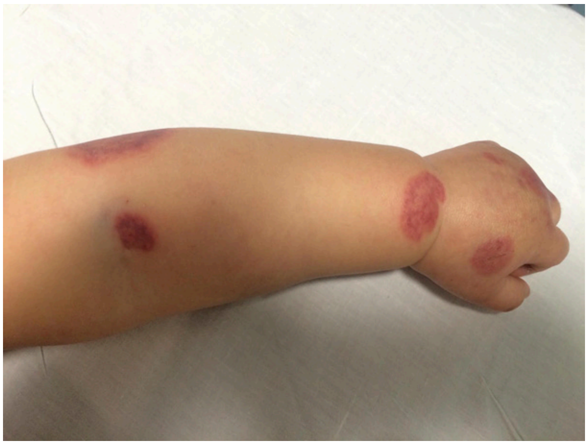

Figure 2. Characteristic targetoid lesions present on the patient's left arm.

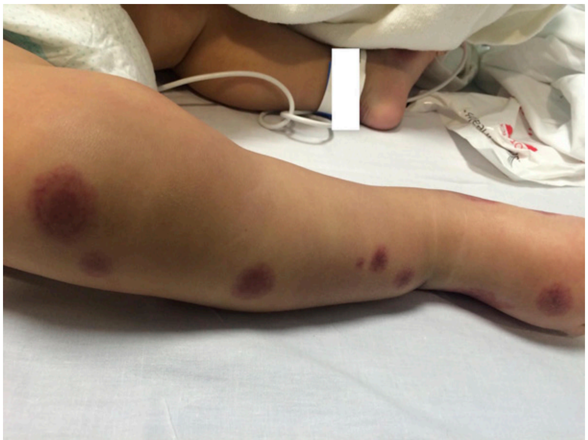
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Figure 3. Characteristic targetoid lesions present on the patient's right leg.

The classic clinical triad in AHEI consists of fever, large purpuric skin lesions, and tender edema. It typically occurs in children aged 4 months to 3 years. Although AHEI is considered by some to be a variant of Henoch-Schonlein purpura (HSP), the characteristic rash and localization of the dermatologic manifestations of these vasculitides vary. In contrast to HSP, the AHEI rash typically manifests as multiple targetoid and purpuric lesions of varying sizes that primarily involve the face, ears, and extremities. The lesions in AHEI do not localize to dependent areas of the body like they do in HSP. Periorbital edema, orchitis, epididymitis, mucosal involvement, hematuria, and hematochezia have all been reported. To our knowledge, there are no previous reports of hemolacria displayed by a patient with AHEI.

Unlike HSP, AHEI does not commonly cause intussusception, renal disease, or other complications, although acute renal failure has been reported and is theoretically possible given the similarities to HSP. Proteinuria increases the concern for renal disease. Complete recovery is expected within 1 to 3 weeks after initial presentation, and recurrence is very rare.

A thorough patient history and identification of the clinical manifestations of AHEI are sufficient for diagnosis. Laboratory evaluations may show leukocytosis, an elevated erythrocyte sedimentation rate, thrombocytosis, and eosinophilia. Biopsies of the cutaneous lesions will show a leukocytoclastic vasculitis. Immunofluorescence may display C3, C1q fibrinogen, or immunoglobulin depositions in the endothelium.

Differential Diagnosis

Other alternate diagnoses to consider include HSP, meningococcemia, disseminated intravascular coagulopathy (DIC), Kawasaki disease, and serum sickness. Meningococcemia and DIC secondary to sepsis should be considered when a purpuric rash is present in the context of an active infection. Disseminated intravascular coagulopathy is a consumptive process and, therefore, thrombocytopenia is expected. However, the patient's platelet count was within normal limits, thereby making DIC unlikely. The patient was afebrile by history, with a low-grade fever during hospitalization, and he was not toxic appearing as would be expected in a child with meningococcemia. Despite edematous extremities and bilateral conjunctivitis, he did not fulfill the diagnostic criteria for Kawasaki disease. Although serum sickness is a reasonable diagnosis to consider in a child presenting with a rash 2 weeks after recent treatment with antibiotics, the characteristic targetoid and hemorrhagic appearance of his rash is more typical of AHEI.

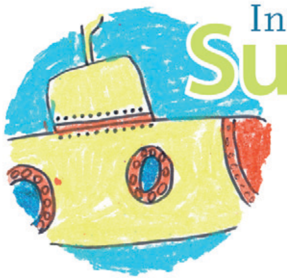
Management

Conservative, symptomatic management is recommended when caring for a patient with AHEI. The efficacy of corticosteroids, antibiotics, and antihistamines is controversial, and further investigations are needed.

Lessons for the Clinician

- The clinical triad of acute hemorrhagic edema of infancy (AHEI) includes low-grade fever; palpable, nondependent, purpuric rash on the face, trunk, and extremities; and tender edema.
- Mucosal involvement can manifest as hemolacria, hematuria, hematochezia, conjunctivitis, oral lesions, and nasal congestion.
- Despite the acuity of onset and dramatic rash, AHEI is largely a benign, self-limiting condition that resolves in 1 to 3 weeks, warranting conservative symptomatic management.
- Renal disease is reported, and periodic urinalysis for several months, similar to what is done for Henoch-Schonlein purpura, is a reasonable approach to follow-up.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/39/8/418.



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3 Emesis and Oral Hyperpigmentation in a 17-year-old Girl

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AUTHOR DISCLOSURE Drs Fredette and Topor have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old girl presents for evaluation of persistent emesis and an unintentional 13.2-lb (6-kg) weight loss during the past 3 months. Emesis occurs daily in the mornings and is nonbloody and nonbilious. Nausea improves throughout the day and with hot showers. She denies diarrhea. When eating, she prefers salty foods such as pickles. She reports daily marijuana use. She feels that marijuana has stained her lips and tongue, as they appear darker to her. She notes fatigue, epigastric pain, weakness, and dizziness. She denies fevers, dysuria, or headaches.

On physical examination she is afebrile, with a heart rate of 140 beats/min, respiratory rate of 18 breaths/min, blood pressure of 86/52 mm Hg, and oxygen saturation of 98%. Her weight is 91 lb (41.3 kg) (<1st percentile), height is 59 in (150 cm) (2nd percentile), and body mass index is 18.3 (14th percentile). Patchy hyperpigmentation is noted on the lips, buccal mucosa, and palate. Bowel sounds are hyperactive, and abdominal examination is without tenderness, rebound, or guarding. There are no masses or hepatosplenomegaly.

Laboratory evaluation reveals a low serum sodium level of 130 mEq/L (130 mmol/L), with a normal potassium level of 3.8 mEq/L (3.8 mmol/L). Urine pregnancy test result is negative. The results of thyroid function testing, liver enzymes, lipase, complete blood cell count, and inflammatory markers are within normal limits. Abdominal radiograph is normal. Additional laboratory testing reveals the diagnosis.

DISCUSSION

Random serum cortisol and corticotropin samples were sent in the setting of hypotension and tachycardia, and a stress dose of hydrocortisone (90 mg/m^2 per day) was administered given concern for primary adrenal insufficiency (PAI). She received normal saline intravenous fluids for volume resuscitation. Her serum cortisol level was low at 1.3 μg/dL (35.9 nmol/L) (normal range, 5.5–20 μg/dL [151.7–551.8 nmol/L]), and her corticotropin level was elevated at 3,156 pg/mL (694 pmol/L) (normal range, 9–57 pg/mL [2–13 pmol/L]), diagnostic of PAI.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for recurrent emesis, abdominal pain, and weight loss with associated symptoms of fatigue and weakness is vast and includes conditions such as pregnancy, eating disorders, acute infections or inflammatory disorders, gastrointestinal obstruction or gastroparesis, cyclic vomiting syndrome, cannabinoid hyperemesis syndrome, increased intracranial pressure, and adrenal insufficiency. Our patient had a history of frequent marijuana use and improvement in nausea with hot showers, which supports a diagnosis of cannabinoid hyperemesis syndrome. However, her findings of oral hyperpigmentation, salt craving, and electrolyte abnormalities were worrisome for an alternative diagnosis of PAI. Cannabinoid hyperemesis is a syndrome of severe cyclic vomiting accompanied by abdominal pain in individuals who use marijuana frequently. Symptoms are temporarily alleviated by hot showers and baths, and patients may report compulsive bathing for symptom relief. The pathophysiology is unclear, but proposed mechanisms include dysregulation in endogenous cannabinoid receptors in the brain and gastrointestinal tract. Definitive treatment is abstinence from cannabis use. (1)

Hyperpigmentation of the oral cavity is classically seen in PAI, but it can also be physiologic. (2) Physiologic oral hyperpigmentation occurs in dark-skinned individuals and darkens with age and with smoke exposure. Tobacco smoke exposure itself can cause hyperpigmentation, typically seen in the gingiva. Oral hyperpigmentation can also be seen as a postinflammatory reaction to oral infections or trauma or after foreign body exposure to lead or amalgam. (3) Peutz-Jeghers syndrome is associated with mucocutaneous hyperpigmentation but is accompanied by intestinal polyposis and increased cancer risk. Most individuals with this autosomal dominant clinical syndrome have mutations found in the tumor suppressor gene *STK11* and have a higher risk of intraintestinal and extraintestinal malignancies, including gastrointestinal, breast, ovarian, pancreatic, cervical, testicular, and lung cancers, among others. These individuals are also at risk for severe bleeding, obstruction, and intestinal infarction due to large numbers of hamartomatous polyps in the gastrointestinal tract, most commonly in the small intestine. In this condition, blue to black macules are characteristically seen on the vermilion border of the lower lip but are also found intraorally and periorally on the hands and feet, as well as surrounding the eyes, nose, and perianal region. Macules are not present at birth, typically appear in infancy, and often fade during puberty. Intraoral macules often persist into adulthood. (4)

THE CONDITION

Primary adrenal insufficiency, commonly referred to as Addison disease, results from the failure of the adrenal cortex to produce adequate cortisol and aldosterone. The signs and symptoms can be nonspecific, with insidious onset including fatigue, weight loss, mood changes, abdominal pain, nausea, vomiting, and weakness. Salt craving, as well as electrolyte abnormalities, including hyponatremia, hyperkalemia, hypercalcemia, and hypoglycemia, can be present. In women, axillary and pubic hair may be sparse due to low adrenal androgen production.

Low cortisol levels in PAI stimulate production of corticotropin and other pro-opiomelanocortin cleavage products, such as melanocyte-stimulating hormone. An elevated melanocyte-stimulating hormone level triggers melanin production, resulting in the classic hyperpigmentation of the skin and mucous membranes found in PAI. Hyperpigmentation is typically generalized but is most easily identified in mucous membranes, skin creases, and scars. With treatment, the corticotropin levels decline, and the diffuse hyperpigmentation typically improves. (5)

In contrast, secondary adrenal insufficiency is due to insufficient corticotropin production, which leads to cortisol deficiency without hyperpigmentation. Salt craving and hyperkalemia are also absent in secondary adrenal insufficiency, as aldosterone production is intact.

Up to 90% of adult patients in developed countries with PAI have autoimmune adrenalitis, diagnosed with autoantibodies to adrenal enzymes such as 21-hydroxylase. In pediatrics, genetic forms constitute most cases, the most common being congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Alternate etiologies of PAI include adrenal hypoplasia, X-linked adrenoleukodystrophy, metabolic disorders, infections, infiltrative disorders, neoplasms, and hemorrhage. (6)

The diagnosis of PAI is suggested by a serum morning cortisol level less than 5 μg/dL (<140 nmol/L) in combination with a corticotropin level greater than 2-fold the upper limit of the reference range. If clinical circumstances allow, confirmatory testing with a corticotropin (synthetic corticotropin) stimulation test is used. In the stimulation test, 250 μg of intravenous corticotropin is administered to individuals 2 years or older, 125 μg to individuals younger than 2 years, and 15 μg/kg to infants. (7) Cortisol levels are measured 30 and/or 60 minutes after infusion. Diagnosis of adrenal insufficiency is confirmed if the peak cortisol level is less than 18 μg/dL (<500 nmol/L) 30 or 60 minutes after injection. (7)

Undiagnosed PAI can present acutely in adrenal crisis when a patient is subjected to severe stress, major illness, trauma, or surgery. Adrenal crisis is a life-threatening state with signs including abdominal pain, vomiting, hypotension, severe electrolyte abnormalities, shock, and even death. Treatment of adrenal crisis should not be delayed while awaiting confirmatory results.

MANAGEMENT

Maintenance treatment of PAI requires both glucocorticoid and mineralocorticoid replacement therapy, as well as stress dosing of corticosteroids with acute illness, trauma, or surgery. The typical dose of maintenance glucocorticoid replacement is hydrocortisone 8 to 10 mg/m^2 per day divided 3 times daily. Typical stress dosing is hydrocortisone 50 to 100 mg/m^2 per day divided 4 times daily and administered every 6 hours. During stress dosing, maintenance glucocorticoid and mineralocorticoid replacement is held. Typical mineralocorticoid dosing in the pediatric population is 0.1 to 0.2 mg of fludrocortisone daily. Salt should not be restricted, and in infants, salt supplementation may be required.

PATIENT COURSE

Tachycardia, hypotension, electrolyte abnormalities, and emesis improved within 24 hours of treatment, and she transitioned to maintenance hydrocortisone and fludrocortisone at discharge. She and her family received education about her diagnosis and the indications for stress dosing of corticosteroids.

Lessons for the Clinician

- Oral and skin hyperpigmentation, a specific sign of Addison disease, is a clue to the diagnosis of primary adrenal insufficiency (PAI) in an individual with otherwise vague symptoms, including gastrointestinal complaints, weakness, dehydration, and fatigue.
- Diagnosis of PAI is suggested by a serum morning cortisol level less than 5 μg/dL (<140 nmol/L) combined with a serum corticotropin level greater than 2-fold the upper limit of the reference range. Confirmatory testing is with corticotropin stimulation testing, with peak cortisol levels less than 18 μg/dL (<500 nmol/L) at 30 or 60 minutes.
- Given the life-threatening nature of adrenal crisis, if you are considering adrenal insufficiency with acute adrenal crisis as a top diagnosis on your differential diagnosis list, start treatment with a stress dose of corticosteroids while awaiting diagnostic studies to return, ideally serum cortisol and corticotropin levels.

References for this article are at http://pedsinreview.aappublications.org/content/39/8/421.

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4 Weakness and Headaches in a 14-year-old Boy

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PRESENTATION

A 14-year-old boy presents to the hospital with headache and weakness for the third time in 3 months. One day before hospital admission the patient developed a severe headache that resolved with sumatriptan use. Hours before arriving at the hospital he played basketball for half an hour outside, but on returning home he noticed a worsening throbbing right-sided frontal headache without radiation. Within a few minutes the patient developed progressively increasing weakness in all 4 extremities, which prompted him to lie down. His previous presenting symptoms had included fever, headache, dizziness, blurry vision, stumbling gait, and stiffness, muscle tightness, and a tingling sensation in all 4 extremities. At previous presentations, acute disseminated encephalomyelitis (ADEM) and migraines were suspected, and the patient was started on high-dose (1 g per 24 hours for 5 days) intravenous methylprednisolone, with a prednisone taper, to which he responded very well and symptoms (headaches, dizziness, weakness, ataxia) resolved.

The child was in good health until 3 months ago. His medical history is significant for intermittent asthma, triggered by weather changes, which is well controlled with albuterol and mometasone as needed. Immunizations are up to date. The patient's family moved into a new house approximately 8 months previously. Because the previous owner had many parrots, the house was uninhabitable due to the amount of bird feces, which the patient and his father had to clean before moving in. He has not traveled in the previous 3 years. He was born and raised in Las Vegas, Nevada. He eats home-cooked food that is healthy and well balanced.

Findings from physical examination are benign for the patient. On neurologic examination he is alert and oriented. Cranial nerves II to XII are intact. His sensory and motor function is intact in all extremities. Romberg sign is positive. However, there were no other signs of cerebellar involvement or gait abnormalities present.

DISCUSSION

A range of differential diagnoses was considered for the headache and weakness, including atypical migraine, multiple sclerosis, ADEM, and meningitis.

Brain magnetic resonance imaging (MRI) was performed and was compared with his brain MRI from the previous week. This was a follow-up MRI with the neurologist 3 months after treatment for ADEM. The report is unchanged from the previous brain MRI that showed numerous foci of increased flair and deep white matter to bilateral cerebral hemispheres clustered in frontal and parietal white matter suspicious for demyelinating disease. Findings on MRI of the spine were not significant. He had an interventional radiology–guided lumbar puncture with opening pressure of 16.8 cmH_2O and a cerebrospinal fluid (CSF) cell count showing 1 white blood cell and no red blood cells, with protein and glucose levels elevated at 7.9 g/dL (79 g/L) and 1,838 mg/dL (102 mmol/L), respectively. The CSF Gram-stain showed no white blood cells or organisms, and the culture was negative. Cryptococcal antigen in CSF was positive. Other infectious evaluations performed, including CSF *Aspergillus* antigen, *Coccidiodes* antibody, acid-fast bacillus culture, and fungal culture, were all negative. India ink stain was negative for yeast cells. Serum testing included human immunodeficiency virus antigen/antibody assay negative, cytomegalovirus immunoglobulin (Ig) M negative and IgG positive, *Mycoplasma pneumoniae* antibody negative, IgM negative, and *Toxoplasma* IgM/IgG negative.

With the history of admission and treatment for ADEM, the patient underwent some immune evaluations. Laboratory tests performed included T-cell subsets, CD4 T helper cell subsets, and quantitative immunoglobulins, and the results were all within normal limits. An autoimmune panel had negative findings for antinuclear antibodies, anti-DNA, anti-Jo, anti-SSa/b, anti-Sm, and scleroderma antibody, whereas anti-RNP was mildly elevated. Rheumatoid factor level was within normal limits. The multiple sclerosis panel was negative, and myelin basic protein was within normal limits.

With the laboratory results returning positive for cryptococcal antigen in the CSF as well as white matter lesions on brain MRI, these findings are consistent with cryptococcal central nervous system disease in an otherwise immunocompetent patient. Subsequently, antifungal therapy with intravenous amphotericin B liposome and oral flucytosine is started. The patient was to have repeated CSF studies performed after 2 weeks as per the infectious disease specialist. On repeated CSF testing, culture was negative, fungal culture and India ink staining were negative, and the cryptococcal antigen was negative as well.

THE CONDITION

Cryptococcus neoformans is an encapsulated, yeastlike fungus that is round to oval and approximately 4 to 6 μm in diameter. The yeast has a thick capsule that consists of polysaccharides that protect the fungus from phagocytosis. It is an opportunistic fungus that typically affects patients who are immunocompromised especially those that are HIV positive. *C neoformans* is commonly found in soils visited by birds. It is transmitted via inhalation and deposits in the alveoli causing a range from asymptomatic to progressive pulmonary disease. Symptoms usually have a subacute/chronic course and can include chronic cough, low-grade fever, chest pain, mucoid or bloody sputum, malaise, and weight loss. Due to *C neoformans* affinity for the CNS, it commonly spreads hematogenously to the brain and is the most common cause of fungal meningoencephalitis. Most patients with cryptococcosis of the central nervous system present with signs and symptoms of subacute meningitis, such as headache, irritability, meningismus, fever, cranial nerve palsies, visual disturbances, altered mental status, or seizures over several weeks.

There have been isolated cryptococcomas of the central nervous system that have been previously described in immunocompetent adults. There was 1 similar case report in an immunocompetent child and an infant found in the literature.

DIAGNOSIS

Testing for detection of cryptococcal polysaccharide antigen in serum and CSF is highly specific and more sensitive for diagnosis of invasive disease compared with microscopy and culture. We used the enzyme immunoassay for detection of cryptococcal capsular polysaccharide antigen, which, according to Redbook, the antigen is detected in CSF or serum specimens from more than 98% of patients with cryptococcal meningitis. The MRI shows intraparenchymal lesions. One can expect there to be growth on the fungal culture as well as an elevated white blood cell count with lymphocyte predominance and an elevated protein level. There is often an elevated opening pressure of the CSF greater than 200 cmH_2O. An India ink stain can help visualize the polysaccharide capsule. It appears as a clear halo around the yeast in a black field.

TREATMENT

Standard treatment includes a combination of amphotericin B and flucytosine. The additive effects of this combination has allowed for a decreased amount of amphotericin needed to treat, therefore reducing its toxicity on the patient while also preventing resistance associated with monotherapy. A standard induction dose for liposomal amphotericin B (AmBisome, Astellas Pharma US, Northbrook, IL) and amphotericin B lipid complex at 3 to 6 mg/kg per day have shown treatment successes similar to that of amphotericin B deoxycholate, with reduced toxicity. Our hospital had liposomal amphotericin B available for treatment of our patient. In discussion with the infectious disease and neurology specialists, the team treated the patient with standard induction therapy of amphotericin B and flucytosine for 2 weeks followed by 8 to 10 weeks of fluconazole.

Lessons for the Clinician

- This case was reported to highlight the importance of thorough history taking and critical thinking of differential diagnoses in the presence of unique symptoms.
- This patient gives us a look into an immunocompetent pediatric patient and reminds us that cryptococcal meningitis can occur in immunocompetent children as well.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/39/8/424.

Gonorrheal Diseases

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AUTHOR DISCLOSURE Dr Perry has disclosed that she is a Nexplanon instructor for Merck. Dr Allison has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Home-based versus clinic-based specimen collection in the management of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections. Fajardo-Bernal L, Aponte-Gonzalez J, Vigil P, Angel-Müller E, Rincon C, Gaitán HG, Low N. *Cochrane Database Syst Rev.* 2015;9: CD011317.

The Institute of Medicine (1997) stated that "the scope, impact, and consequences of sexually transmitted infections (STIs) are underrecognized by the public and health-care professionals." *Neisseria* gonorrhea is currently the second most commonly reported communicable disease in the United States. In pediatrics practice, the greatest gonorrhea risk is found in adolescents and young adults, who may become infected during sexual contact, and newborns, who become infected from vertical transmission. The overall prevalence of gonorrhea has increased recently from a low of 98 cases per 100,000 population in 1998 to 124 cases per 100,000 in 2015. Young adults of ages 18 to 24 years have the highest prevalence of gonorrhea infection with a rate of approximately 400 cases per 100,000. In addition to age, there are disparities in prevalence based on race, ethnicity, poverty, and sexual orientation.

Neonatal gonorrhea is very uncommon in high-resource countries, as routine prenatal screening for gonorrhea and newborn administration of erythromycin ophthalmic ointment have become standard care. Neonatal gonorrheal infection commonly presents 2 to 7 days after birth as ophthalmia neonatorum with symptoms of bilateral conjunctival mucopurulent discharge and hyperemia as well as eyelid edema. Ophthalmia neonatorum has up to a 16% risk of corneal scarring and blindness if untreated. Other potential manifestations of neonatal gonorrhea include scalp abscesses (if scalp electrodes are used in an infected birth canal) and possible subsequent disseminated gonorrheal infection, manifested as polyarticular disease, bacteremia, and meningitis.

Adolescents are at increased risk of developing gonorrhea and other STIs due to several biological, social, and behavioral factors, such as cervical ectopy, immature genital mucosal immunity, limited access to confidential care, inconsistent condom use, and alcohol or drug use associated with sexual activity. Adolescents with early puberty and age-discordant partners are at even higher risk. Approximately 10% of infected men and up to 95% of infected women are asymptomatic during infection. Among men with symptomatic genitourinary infection, symptoms typically develop 2 to 7 days after initial infection but can start up to 30 days later. Although urethritis is the most common presentation, epididymitis and/or prostatitis can also occur. Symptomatic women develop symptoms 5 to 10 days after initial infection with urethritis or cervicitis. Pelvic inflammatory disease, a common cause of ectopic pregnancy and infertility, can present much later. Extragenital gonorrhea presents as pharyngeal or disseminated infection. Pharyngeal infection is asymptomatic 90% of the time, with exudative pharyngitis noted if symptomatic. Disseminated gonococcal infection (DGI) is a rare (0.4%–3%) complication of untreated gonococcal disease, presenting most commonly as petechial or pustular acral skin lesions, polyarthralgias (large and small joints), tenosynovitis (hands and feet), and oligoarticular septic arthritis (knees, ankles, or wrists). DGI can also be associated with perihepatitis and less commonly with endocarditis, pericarditis, and meningitis.

Screening strategies are important for gonorrhea, because most infections are asymptomatic. Both the Centers for Disease Control and Prevention (CDC) and American College of Obstetricians and Gynecologists recommend annual gonorrhea screening for all sexually active women less than or equal to 25 years "who may be at increased risk." Risk factors include multiple current partners, having a new partner, inconsistent condom use, and sex while under the influence of alcohol or drugs. The US Preventive Services Task Force (USPSTF; grade B) and American Academy of Family Physicians (AAFP) recommend annual gonorrhea screening for all sexually active women less than or equal to 25 years, even if they do not engage in high-risk behaviors. The USPSTF finds insufficient evidence for or against routine gonorrhea screening of asymptomatic sexually active men, because of lower prevalence of asymptomatic infection and less morbidity associated with asymptomatic gonorrhea infections in men. The CDC recommends that routine gonorrhea screening of asymptomatic men be considered in individual clinical settings based on the prevalence or risk of the specific population served. Routine gonorrhea screening is recommended for men who have sex with men (MSM), notably a population in which 64% of gonorrheal disease occurs in rectal or pharyngeal sites. The CDC, AAFP, and USPTF recommend at least annual screening for MSM with specimens obtained from the genital, rectal, and pharyngeal sites.

Endocervical or vaginal culture in women and urethral culture in men remain the gold standard tests but are generally only used if antibiotic susceptibility testing is necessary. Nucleic acid amplification tests (NAAT) and hybridization tests from urine samples are becoming first-line screening tools, because of their higher sensitivity (90%–100%) and comparable specificity (97%) relative to culture. Although the accuracy of NAAT in urine, endocervical, and vaginal specimens is comparable for women, urine NAAT is more sensitive than urethral swab for men. NAAT can also be used for pharyngeal and rectal specimens. However, Gram stain and culture should be used to diagnose gonococcal conjunctivitis. In cases of DGI, specimens should be collected from blood and any other involved sites, in addition to genital sites. Patients with positive results on gonorrhea testing and their partners should be offered screening for chlamydia, trichomonas, human immunodeficiency virus, syphilis, hepatitis B if unvaccinated, and possibly hepatitis C.

Treatment of gonorrhea is complicated by increasing resistance to fluoroquinolones and reduced susceptibility to cefixime worldwide. A 2-agent treatment regimen is recommended for all gonorrheal infections to decrease acquisition of resistance and to treat presumed chlamydia coinfection. The current CDC recommended treatment is single doses of ceftriaxone 250 mg intramuscularly and azithromycin 1,000 mg orally. Alternative regimens are available and should be tailored to the specific type of gonococcal infection, presence of medication allergies, existence of possible medication interactions, and/or limited access to first-line medications (Table). Ideally, all treatments should be administered at the same time under direct observation to ensure complete treatment. Adequate treatment should eliminate symptoms in 3 to 5 days but patients should abstain from sexual activity for 7 days after treatment and until all symptoms are gone. All sexual partners within the past 60 days should also be empirically treated with dual therapy. If it is not possible for the partner to be evaluated, expedited partner therapy packets with 400 mg of cefixime, 1,000 mg of azithromycin, and educational materials can be delivered to the partner by the patient or a disease investigation specialist. Although legal in most regions of the United States, laws and regulations on expedited partner therapy vary by state. Online anonymous partner notification services, such as www.inspot.org or www.dontspreadit.org, may assist individuals when in-person partner notification is not safe or ideal.

Follow-up testing to ensure cure ("test-of-cure") is not required for uncomplicated urogenital or rectal gonorrhea when treated with a recommended treatment regimen. However, NAAT or culture is recommended 7 to 14 days after treatment for all individuals with pharyngeal gonorrhea, given the lower cure rates compared with urogenital and anorectal infection (~90% vs ~99.5%, respectively). All patients with confirmed gonococcal disease of any location should be retested in 3 to 6 months because of the frequency of reinfection. Antibiotic susceptibility testing is indicated if the patient retests positive, to distinguish reinfection from treatment failure.

In addition to consistent screening and appropriate treatment, multifactorial prevention will be the best way to turn the tide of the gonorrhea epidemic. Research on vaccines to prevent *Neisseria* gonorrhea infection is in early stages. Home-based collection to increase screening availability may also reduce transmission rates. A 2015 Cochrane review suggested that home-based collection may be as effective as clinic-based collection for chlamydia and gonorrhea screening. Behavioral change programming for adolescent patients

TABLE. **Recommended and Alternative Therapy for Gonococcal Infections**

INFECTION	RECOMMENDED TREATMENT	ALTERNATIVE REGIMENS
Gonococcal conjunctivitis	Ceftriaxone 1g IM in a single dose PLUS azithromycin 1 g orally in a single dose	
Uncomplicated—cervix, urethra, rectum	Ceftriaxone 250 mg IM in a single dose PLUS azithromycin 1 g orally in a single dose[a]	If ceftriaxone unavailable Cefixime 400 mg orally in a single dose PLUS azithromycin 1 g orally in a single dose[b]
Uncomplicated—pharynx	Ceftriaxone 250 mg IM in a single dose PLUS azithromycin 1 g orally in a single dose	
If known IgE-mediated penicillin allergy OR if elevated cephalosporin MICs on antimicrobial susceptibility testing	Gemifloxacin 320 mg orally in a single dose PLUS azithromycin 2 g orally in a single dose	Gentamicin 240 mg IM in a single dose PLUS azithromycin 2 g orally in a single dose
Arthritis and arthritis-dermatitis syndrome	Ceftriaxone 1g IM in a single dose PLUS azithromycin 1 g orally in a single dose	Cefotaxime 1g IV every 8 h OR ceftizoxime 1 g IV every 8 h PLUS azithromycin 2 g orally in a single dose
Gonococcal meningitis and endocarditis	Ceftriaxone 1–2 g IV every 12–24 hours PLUS azithromycin 1 g orally in a single dose	
Ophthalmia neonatorum	Ceftriaxone 25-50mg/kg IV or IM in a single dose, Not to exceed 125 mg	

IgE=immunoglobulin E; IM=intramuscular; MIC=minimum inhibitory concentration.

[a] *All pregnant women should be treated with this regimen. If an IgE mediated penicillin allergy, consult an infectious disease specialist.*

[b] *Test of cure should be done one week after to ensure adequate eradication of disease given increased resistance to cefixime.*

Patients positive to the human immunodeficiency virus (HIV) should be treated with the same regimens listed herein as those patients who are HIV negative.

Adapted from sexually transmitted diseases treatment guidelines (2015) from the Centers for Disease Control and Prevention.

incorporates information, education, and communication such as condom use negotiation, and is the most studied prevention style but has produced mixed results. Comprehensive sexual education that includes, but is not limited to, abstinence education has proven to be the most ethical and scientific way to teach adolescents about the risks and prevention of all sexually transmitted infections.

COMMENT: As a pediatrician who works closely with adolescent patients, I found this *In Brief* article helpful in reviewing the importance of knowing best procedures for the screening, timely diagnosis, and treatment of gonorrhea to prevent morbidity to the infected individual and transmission to others. Drs Perry and Allison identify the patient populations who should undergo screening to identify asymptomatic cases, and according to the 2015 article in *Morbidity and Mortality Weekly Reports*, routine screening for men and older women is not recommended because of their lower risk. Healthy People 2020 has set STI reduction goals to which our country should aim, with a goal of "10 percent improvement over baseline." This *In Brief* article is also a good example of the importance of continued education about prevention through visits with health care providers, the school system, public health departments, and social media.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

in Brief

Tetanus Disease, Treatment, Management

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AUTHOR DISCLOSURE Drs Rhinesmith and Fu have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Tetanus is a life-threatening disease caused by the spore-forming, obligate anaerobic bacterium *Clostridium tetani*. This bacterium is abundant worldwide, mainly found in soil and the gastrointestinal tracts of humans and other animals. Disease is caused by the introduction of bacteria through a skin break, most commonly from a contaminated wound, or poor perinatal hygiene and improper cord care in the neonate, with most cases being birth related. Under anaerobic conditions, dormant *C tetani* spores germinate into bacilli. Bacilli produce the endotoxin tetanospasmin, which prevents the presynaptic release of neurotransmitters that inhibit muscle contraction, leading to uncontrolled muscle contraction and clinical spasms.

The incidence of tetanus has dramatically decreased worldwide since the mid-20th century, largely due to the development and implementation of the tetanus toxoid vaccine. Nonetheless, tetanus remains a significant cause of mortality in the developing world, causing an estimated 56,000 deaths annually worldwide (2015 estimate), approximately 20,000 of them in neonates. The majority of tetanus cases occur in South Asia and sub-Saharan Africa. In the United States, incidence is 0.01 per 100,000, with approximately 10% of cases occurring in patients younger than 20 years.

Tetanus has 4 clinical presentations: neonatal, localized, cephalic, and generalized. Neonatal tetanus generally occurs 3 to 7 days after delivery. Difficulty feeding, poor suck/swallow, and excessive crying often precede overt spasms. Localized tetanus involves muscle contraction limited to the area of injury. Cephalic tetanus, while quite rare, can be associated with head lesions or chronic otitis media; it generally presents with cranial nerve palsy 1 to 2 days after infection. Both localized and cephalic tetanus can progress to the generalized form. Generalized tetanus is the classic form of the disease and accounts for more than 80% of cases. It has a gradual onset approximately 3 to 21 days after the infection, with symptoms typically worsening over a week. Symptoms start with spasms of the masseter muscle, resulting in trismus and lockjaw. Spasms spread cephalocaudally from the head and neck to the trunk and can last for several weeks. Classic findings include *risus sardonicus*, a grimace caused by facial muscle contractions, and *opisthotonus*, a spastic, backward arching of the head, neck, and spine. Reflex spasms are triggered by sensory stimuli. Death can occur quickly from laryngospasm or diaphragmatic spasms. Autonomic dysfunction in the form of labile blood pressure, arrhythmia and temperature instability can also be seen, and patients can develop complications such as rhabdomyolysis.

Diagnosis of tetanus is entirely based on historical and clinical findings; thus, accurate identification can be challenging for clinicians who may have never encountered a single case over the course of a career. The World Health Organization (WHO) case definition of neonatal tetanus is the loss of suck and cry between 3 and 28 days after birth, along with the development of rigidity or

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Mortality from tetanus between 1990 and 2015: findings from the global burden of disease study 2015. Kyu HH, Mumford JE, Stanaway JD, et al. *BMC Public Health.* 2017;17:179. doi:10.1186/s12889-017-4111-4.

spasms in an infant with normal suck and cry in the first 2 days after birth. The WHO case definition of non-neonatal tetanus requires trismus, *risus sardonicus,* or painful muscular contractions along with a history of a wound or injury. The "spatula" test has 94% sensitivity and 100% specificity for diagnosing tetanus clinically. In this test, the posterior wall of the pharynx is stroked with a soft instrument. A positive test result is defined as a reflex spasm of the jaw. Before making a diagnosis of tetanus in a patient, the clinician should exclude other causes of spasms such as hypocalcemia, drug or toxin exposure or conversion disorder.

Treatment of tetanus involves providing supportive care for symptoms of muscle spasms and potential respiratory compromise, neutralizing the remaining tetanus toxoid antibodies, and eradicating bacteria at the wound site. Without treatment, the case fatality rate remains near 100%, even in resource-rich areas. With treatment, case fatality rates drop to 10% to 20%. For generalized tetanus, modern intensive care, including endotracheal intubation, mechanical ventilation, deep sedation, and/or paralysis is the mainstay of supportive care. Patients should have minimal environmental stimulation to avoid reflex spasms. Benzodiazepines, particularly diazepam, are treatments of choice, because they provide sedation, control muscle spasm, and provide anxiolysis. Intravenous magnesium sulfate can be used as an adjunct antispasmodic agent that also decreases autonomic instability. Intrathecal baclofen has shown promise for severe spasms, but may not be feasible in resource-poor areas where intrathecal catheter insertion is not practical and mechanical ventilator support is unavailable, because higher doses can cause respiratory depression and cardiovascular instability. Autonomic instability can be treated with clonidine, β-blockers, and morphine.

Other components of tetanus treatment include administration of human tetanus immune globulin (TIG) as a single intramuscular injection as soon as the diagnosis is made. TIG prevents disease progression by binding unbound tetanus toxin, but is not a reversal agent. Ongoing wound care, including prompt cleaning and debridement of necrotic tissue, is essential to limit bacterial growth after infection. Antibiotics, particularly penicillin or metronidazole, may prevent disease progression by killing tetanus bacilli, thereby preventing creation of more tetanoplasmin.

Tetanus disease can never be completely eradicated because the bacteria maintain natural reservoirs in soil, humans, and other animals. Furthermore, there is no naturally acquired immunity; the very small amount of toxin necessary to cause disease does not stimulate antibody production in the host. However, tetanus is almost entirely vaccine preventable because the efficacy of the vaccine is virtually 100%. A 6-dose series of tetanus toxoid–containing vaccine (TTCV)—which includes 3 doses in the first year after birth, followed by booster doses in the second year, in early childhood, and in adolescence—has been shown to provide immunity and protect women through their childbearing years, though some countries still endorse a 5-dose series.

Maternal tetanus vaccination prevents neonatal tetanus by passing maternal antibodies through the placenta. In the developing world, vaccination campaigns targeting women of childbearing age have reduced neonatal tetanus mortality by 94%. In the United States, regardless of prior TTCV vaccination history, all pregnant women are recommended to receive 1 dose of TTCV between the 27th and 36th weeks of pregnancy, preferably on the earlier side of that range. Any unvaccinated or undervaccinated woman should complete a full 3-dose series during pregnancy.

TTCV and/or immune globulin should be used for prevention in the event of a wound in an inadequately vaccinated host. For patients with a clean, minor wound, TTCV should be given if immunization status is unknown or unreliable, the initial series was never completed, or the last booster dose was received 10 or more years earlier. TIG is unnecessary for clean or minor wounds. For patients with a major wound, a puncture wound, a burn or crush injury, or a contaminated wound, both TTCV and TIG should be given if immunization status is unknown or incomplete. For those with this type of wound who have completed the original vaccine series, a TTCV booster dose should be given if the last booster was given 5 or more years earlier.

Although *C tetani* will never be completely removed from the environment, human disease can be minimized with improved tetanus vaccine availability, enhanced wound care, and improvement in neonatal care worldwide.

COMMENTS: This *In Brief* article by Drs Rhinesmith and Fu reviews important concepts in diagnosis, treatment, and prevention of tetanus. As mentioned, while rare in high-resource communities, I had never cared for a patient with tetanus in the United States, but I did encounter 2 cases in sub-Saharan Africa. The first was a neonate who unfortunately died, and the second was a toddler-aged child who fell in a fire and developed tetanus in his wound. He fortunately survived. This topic demonstrates the amazing benefit of timely and complete immunizations, something easier to accomplish in the United States than in some resource-poor countries.

The tetanus vaccine was produced in 1924 and used for soldiers in World War II. Thanks to vaccine development it can be used in children, pregnant women, and adults. As noted, even when someone develops tetanus he/she does not develop lifelong immunity, so complete immunization is essential. There is no person-to-person transmission so there isn't the development of herd immunity which can occur with vaccines due to communicable diseases. A few medical literature resources comment on the possibility of those who perform self-piercing or self-tattooing to develop tetanus, so consider questioning to assess these risk factors when the possibility of tetanus must be considered.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

ANSWER KEY FOR AUGUST 2018 PEDIATRICS IN REVIEW

Group A *Streptococcus*: 1. E; 2. C; 3. C; 4. B; 5. C.

Pediatric Esophageal Disorders: Diagnosis and Treatment of Reflux and Eosinophilic Esophagitis: 1. D; 2. D; 3. B; 4. D; 5. E.

Common Substances of Abuse: 1. A; 2. D; 3. E; 4. D; 5. C.

Visual Diagnosis

A 7-year-old Boy with Dyspnea and an Unusual Chest Radiograph

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PRESENTATION

A 7-year-old boy presents to his pediatrician with gradually worsening shortness of breath and exercise intolerance over months to years. He was admitted for right-sided pneumonia twice during childhood with seemingly complete recovery each time, but otherwise he has been generally healthy and developmentally appropriate. Current medications include albuterol inhalers taken as needed since early childhood for wheezing during viral illnesses. With the recent worsening of his symptoms, albuterol is again tried without any improvement in his symptoms. He does not have fever, cough, nasal congestion, chest pain, palpitations, vomiting, diarrhea, or weight changes.

On physical examination, the patient has normal vital signs. He is small for his age but is following his growth curve appropriately with height in the 15th percentile and weight in the 11th percentile. He has normal findings on head and neck examination. His cardiac examination is notable for a fixed split S2 with no murmurs, rubs, or gallops. He has diminished breath sounds on the right with a soft, intermittent

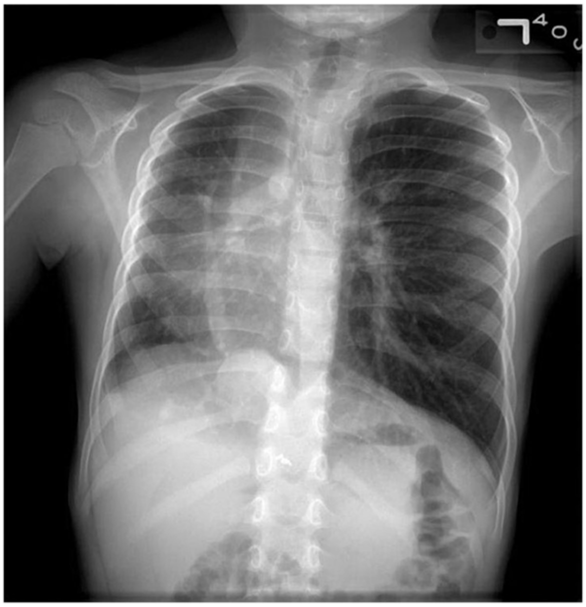


Figure 1. Chest radiograph interpreted as dextrocardia, prominent right-sided pulmonary vasculature, and hyperinflation of the left lung.

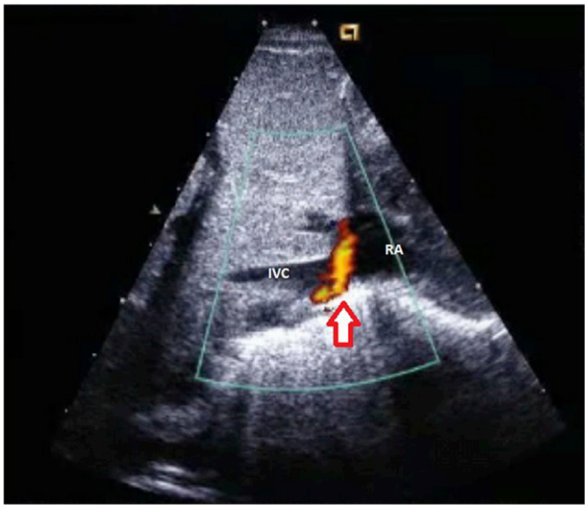
AUTHOR DISCLOSURE Drs Salciccioli, Qureshi, and Allen have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

expiratory wheeze and a clear left lung. He has no abdominal organomegaly. Pulses are 2+ and symmetric in all extremities.

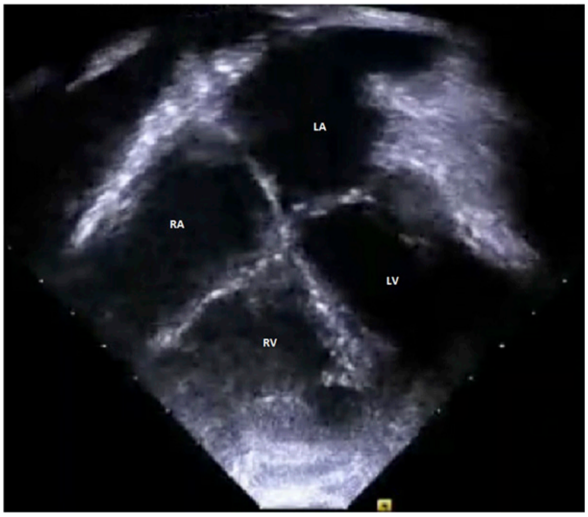
In addition to his physical examination findings, a chest radiograph (Fig 1) is interpreted as showing dextrocardia, so the patient is referred to the cardiology clinic where echocardiography reveals the diagnosis.

DIAGNOSIS

In the cardiology clinic, echocardiography shows the heart located in the right chest, with the cardiac apex pointing leftward, partial anomalous venous return to the inferior vena cava (IVC) (Video 1), and mild right heart dilation (Video 2).

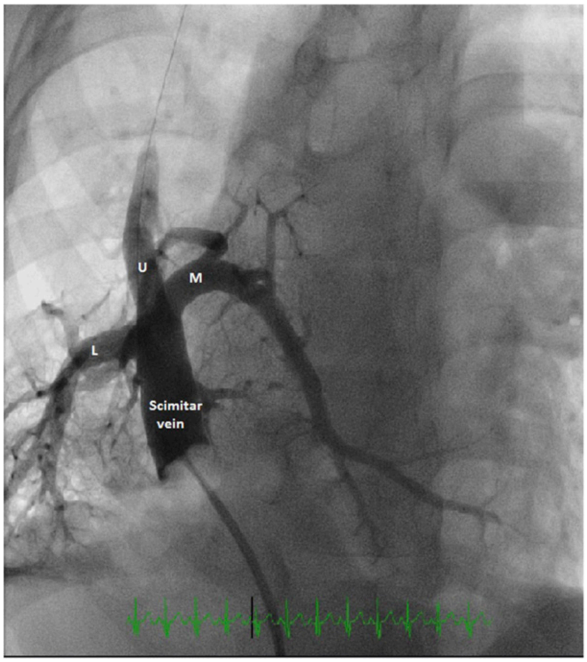


Video 1. In this subcostal echocardiographic clip, the red flow (arrow) shows venous drainage into the intersection of the inferior vena cava (IVC) and the right atrium (RA). Subsequent Doppler interrogation of the red flow was consistent with pulmonary venous flow.

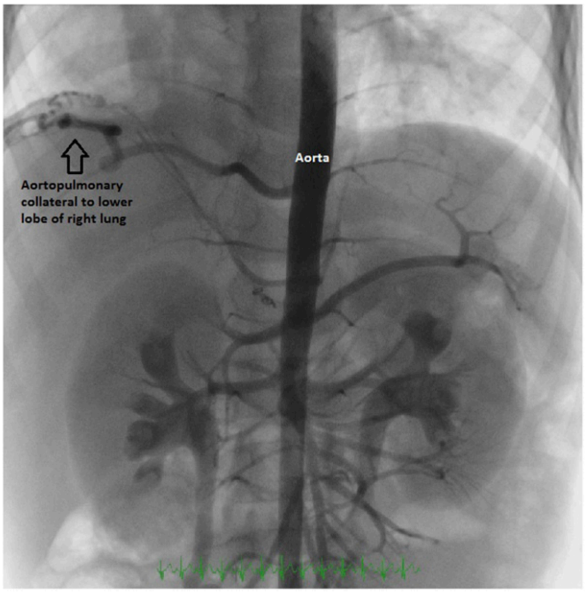


Video 2. An apical 4-chamber echocardiographic clip shows mild right heart dilation, with the right atrium (RA) and right ventricle (RV) larger than the respective left-sided chambers.

Based on these findings, the patient is scheduled for cardiac catheterization. The diagnosis is confirmed with angiography. Video 3 shows a catheter accessing the final common anomalous pulmonary vein from its insertion to the inferior vena cava with contrast showing the branches from each right lung lobe. Video 4 shows a moderate-sized



Video 3. Contrast is injected into the scimitar vein, showing that all 3 right pulmonary veins—upper (U), middle (M), and lower (L)—drain to the common anomalous vein. Balloon deflation shows the veins draining unobstructed into the right atrium-inferior vena cava junction.



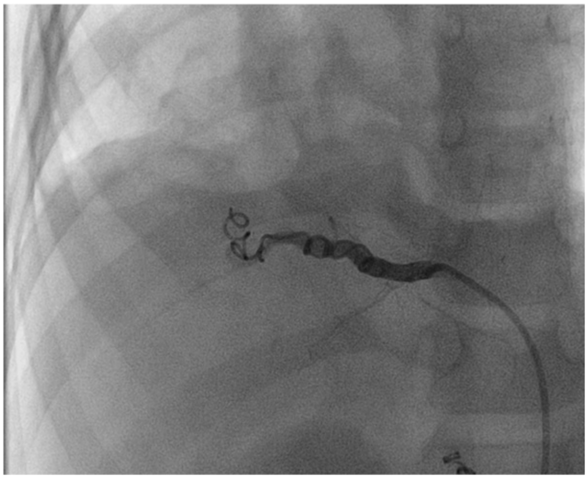
Video 4. Contrast injection into the descending aorta shows an aortopulmonary collateral to the lower lobe of the right lung.

aortopulmonary (AP) collateral arising from the abdominal aorta which feeds a segment of the right lower lobe. This collateral is subsequently occluded with coils (Video 5).

DISCUSSION

The constellation of right lung hypoplasia with secondary dextroposition of the heart, right-sided partial anomalous pulmonary venous return (PAPVR) to the right atrial–IVC junction, and AP collaterals from the abdominal aorta to a sequestered lobe of the right lung is consistent with a diagnosis of scimitar syndrome.

A scimitar is a curved Turkish sword that was used throughout the Middle East from the 12th to the 16th centuries (Fig 2). This patient's chest radiograph is classic, with the large common pulmonary vein draining the right lung, forming the characteristic scimitar shape along the right heart border (Fig 3). (1) The right lung is hypoplastic, leading to secondary dextroposition of the heart; the heart is normal shaped with the apex leftward, but because of the right lung hypoplasia, it is shifted rightward and gives the impression of dextrocardia on plain film radiography. In addition, there is compensatory hyperinflation of the left lung. Independent of the clinical history, a similar chest radiograph alone should prompt consideration of the diagnosis.



Video 5. After coiling, no flow is seen to the lower lobe of the right lung via the aortopulmonary collateral.

Figure 2. Example of a scimitar, a curved blade used in the Middle East in the 12th to 16th centuries. (Scimitar courtesy of Mark Kline, MD; photograph by Katherine Salcicciolі, MD.)

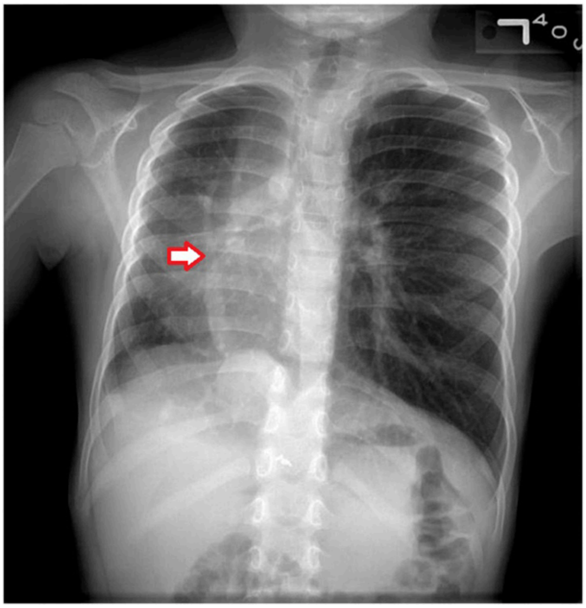


Figure 3. Classic chest radiograph of scimitar syndrome showing the scimitar vein (arrow) with cardiac dextroposition, right lung hypoplasia, and left lung hyperinflation.

Scimitar syndrome was first described as the "imperfect development of the right lung and transposition of the heart" in 1836 by Dr George Cooper. The "scimitar-shaped vein" was noted by Halasz et al in 1956, but the full constellation of anomalies was not formally described as scimitar syndrome until Dr Catherine Neill coined the description in 1960. (2)

Currently, scimitar syndrome is understood to be the sequela of abnormalities of development of the right lung bud during embryology. Within 30 days after conception, the primitive right and left lung buds develop and associate with the splanchnic plexus. Around day 32, this endodermal splanchnic plexus tissue migrates toward the mesodermal common atrium and the connection that forms the pulmonary veins. (3) In scimitar syndrome, the abnormal right lung bud does not normally associate with the splanchnic plexus and therefore does not migrate to meet the cardiac tissue. As a result, the pulmonary veins from the abnormal right lung remain connected to the right-sided structure that will eventually develop into the IVC. In addition to hypoplasia of the right lung, often areas of lung tissue are not connected to the bronchial tree; these are referred to as *areas of sequestration*. As the branches of the pulmonary artery follow the bronchial tree, these areas are also not connected to the right pulmonary artery and subsequently become supplied by AP collaterals, usually from the descending abdominal aorta. (2)

Scimitar syndrome can present in different ways at different ages depending on the severity of the anomalies, and require different interventions.

- Infants: Early symptoms are almost exclusively related to congestive heart failure because of overcirculation from a large burden of AP collaterals. These vessels fill the lung with flow at systemic blood pressures and can lead to failure to thrive and respiratory distress. Intervention is often necessary within the first months after birth and consists of either surgical ligation of the collaterals via an abdominal incision or occlusion of the collaterals using coils or plugs in the cardiac catheterization laboratory. (4) Given the usual hypoplasia of the right lung, the amount of excess flow secondary to the anomalous pulmonary veins is rarely significant enough to cause symptoms. (5) Repair of the anomalous pulmonary veins is usually delayed until the children are older because of the risk of postoperative pulmonary vein stenosis, with complete surgical repair in smaller patients. (4) Other infants may have primary pulmonary hypertension secondary to abnormal vasculature in the right lung, which requires aggressive medical therapy. (6)
- School-age children: Children who do not exhibit symptoms of large AP collateral burden in infancy often present with respiratory issues related to either pulmonary sequestration or, less commonly, overcirculation resulting from a combination of AP collaterals and anomalous pulmonary venous drainage. Children may have recurrent respiratory infections because of the sequestered portions of lung or other areas of bronchial stenosis, which are predisposed to developing postobstructive pneumonia. These patients at times need to have surgical resection of the sequestered lung segments. (6) Children with hemodynamically significant left-to-right shunting will usually have evidence of right heart dilation on echocardiography, which should prompt referral to the cardiac catheterization laboratory for investigation. (3) If found, AP collaterals can be coiled. In addition, calculation of the relative amount of pulmonary blood flow helps identify the appropriate time to refer for pulmonary vein reimplantation. (1)
- Adolescents and adults: Patients are often asymptomatic and diagnosed incidentally on imaging performed for other reasons. Occasionally, they may have evidence of right heart dilation or early pulmonary hypertension, indicating a need for surgical repair of the anomalous pulmonary veins. Usually, however, intervention is not needed acutely, and these patients can be monitored over time. (6)

Overall, scimitar syndrome includes a spectrum of pathophysiology and various clinical presentations, some of which necessitate intervention. The classic chest radiograph should prompt a referral for echocardiography.

PATIENT COURSE

After his procedure in the cardiac catheterization laboratory, the patient had low-grade fevers and chest pain overnight, which were attributed to ischemia from the portion of lung that had previously been supplied by the coiled AP collateral. He did well and was discharged from the hospital the following morning. Over the next few weeks, his mother noted mild improvement in his exercise tolerance, though it was still abnormal. At the time of this writing, he was awaiting elective cardiac surgery for repair of his PAPVR.

Summary

- Scimitar syndrome occurs as a result of abnormal embryologic development of the right lung bud and usually includes:
  - Right lung hypoplasia with secondary cardiac dextroposition.
  - Right-sided PAPVR draining to the right atrial–IVC junction via the “scimitar” vein.
  - AP collaterals from descending abdominal aorta to right lung lower lobe.
  - Pulmonary sequestration.
- Infants present with symptoms of pulmonary overcirculation secondary to AP collateral flow.
- School-age children present with respiratory symptoms secondary to pulmonary hypoplasia and/or sequestration or with milder evidence of pulmonary overcirculation secondary to PAPVR and/or AP collateral flow.
- Teenagers and adults are often incidentally discovered but may have right heart dilation from PAPVR drainage and/or AP collaterals.
- Surgical repair of PAPVR has good results. Pulmonary vein stenosis is probably less common when surgery is delayed until patients are older, so temporizing procedures such as surgical ligation or catheterization laboratory occlusion of collaterals is beneficial for symptomatic younger patients.

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Visual Diagnosis

Newborn with Respiratory Distress

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PRESENTATION

This is the case of a small-for-gestational age (1,455 g) girl born at 35 weeks. She is twin B of a monochorionic, diamniotic twin gestation, born via induced vaginal delivery for acute-onset oligohydramnios in the setting of intrauterine growth restriction. The maternal medical history is significant for depression, idiopathic hypothyroidism (treated with levothyroxine during pregnancy), and obesity. Maternal serologies were negative. Results of routine prenatal echocardiography were normal. After routine resuscitation, the infant receives respiratory support via humidified high-flow oxygen via nasal cannula and umbilical venous catheterization (UVC) for parenteral nutrition. The infant is weaned to room air and continued on a combination of parenteral and enteral nutrition going into the third day of life. At 50 hours after birth, the patient develops acute respiratory distress.

The physical examination is remarkable for signs of respiratory distress, including tachypnea, hypoxemia, nasal flaring, and decreased breath sounds on auscultation (specifically in the right lower lung fields). She has distant heart sounds, no murmur, normal pulses and capillary refill, and a soft, nondistended abdomen. Laboratory evaluation includes a white blood cell count of 7,400×/μL (7.4×10^9/L), a hematocrit value of 53%, a platelet count of 215×10^3/μL (215×10^9/L), a capillary blood gas sample (pH of 7.18, partial pressure of carbon dioxide of 64 mm Hg, partial pressure of oxygen of 32 mm Hg, bicarbonate of 22 mEq/L [22 mmol/L], base deficit of 7.3 mEq/L [7.3 mmol/L]), and a C-reactive protein level less than 0.3 mg/L (<2.9 nmol/L). In summary, she has acute, uncompensated respiratory acidosis with hypoxemia and normal inflammatory markers.

A supine chest radiograph (Fig 1) is obtained and the diagnosis is made.

DIAGNOSIS

The chest radiograph shows a moderate to large right-sided pleural effusion. Further laboratory evaluation of the pleural effusion after thoracentesis demonstrated high triglycerides, an elevated glucose level, a low protein level, and a high cell count, with neutrophil predominance consistent with extravasation of parenteral nutrition. Although a chylothorax can present similarly, it does not involve the pericardial space and is classically characterized by high triglycerides, low glucose levels, elevated protein levels, and lymphocytic predominance. Thus, the clinical presentation, laboratory examination, and radiographic findings are

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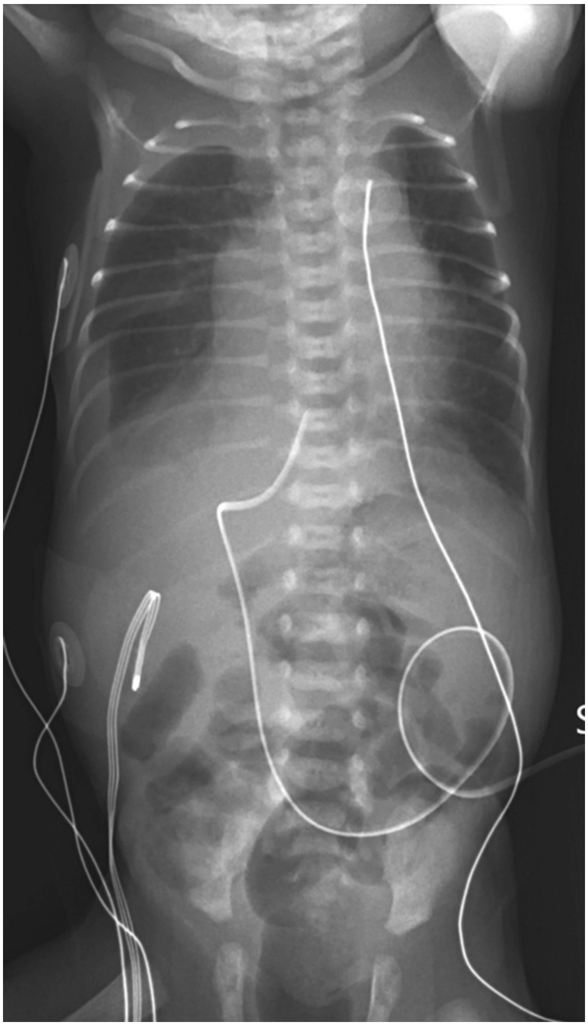

Figure 1. Chest radiograph obtained after the onset of respiratory distress that demonstrates the stable position of umbilical venous catheterization, new-onset moderate to large right-sided pleural effusion and right lung base opacification, small left-sided pleural effusion, and enlarged cardiac silhouette.

consistent with iatrogenic, neonatal pleural effusions and pericardial effusion. This represents a rarely described complication of an appropriately placed UVC.

DISCUSSION

Pleural effusions are rare in the neonatal period and reflect a combination of iatrogenic and congenital causes. Briefly, a pleural effusion is a collection of fluid between the pleural membranes separating the chest wall and the lung parenchyma. Fluid accumulates if the rate of reabsorption is less than the rate of accumulation. Reabsorption rates are influenced by many factors, including hydrostatic pressure, oncotic pressures, lymphatic pressure, and the presence of local inflammation. Estimations of the incidence of pleural effusions in the neonatal population have ranged from 0.05% to 2.2%. In this population, effusions, whether acquired or iatrogenic, occur approximately twice as often compared with congenital effusions.

The clinical presentation of pleural effusions depends primarily on the size of the effusion. Smaller effusions are less likely to be symptomatic, whereas larger effusions are space-occupying lesions that will restrict normal lung movement and may affect development if present in the prenatal period. Patients will present with respiratory distress, including tachypnea, retractions, and hypoxemia, prompting further evaluation. Although these signs are nonspecific, there are classic findings on chest radiographs. Radiographs will demonstrate blunting of the costophrenic angle, fluid in the fissures, and/or mass effect with contralateral mediastinal shift or formation of a meniscus. Nonetheless, ultrasonography is much more sensitive in identifying fluid in the pleural space and can detect volumes as small as 3 mL. Additional testing can be performed on samples of the pleural fluid, which includes measuring pH, cell counts, protein, glucose, lactate dehydrogenase, and triglycerides that can aid diagnosis by distinguishing exudative versus transudative effusions. Light's criteria can be used to differentiate each type of effusion. Exudative effusions are cloudy, with specific gravity more than 1.020, elevated protein content, and lactate dehydrogenase levels higher than two-thirds the upper limit of normal serum levels. Whereas transudative effusions are typically clear in appearance with a specific gravity less than 1.012, protein content less than 2.5 g/dL or fluid to serum ratio less than 0.5, and a lactate dehydrogenase level lower than two-thirds the upper limit of normal serum levels.

Chylothoraces, or lymph accumulation in the pleural cavity due to obstruction or disruption of the thoracic duct, are the most common type of exudative pleural effusions. Chylothoraces can be subcategorized into 3 subtypes: primary or congenital, posttraumatic, and nontraumatic. Congenital chylothorax is associated with Turner, Down, and Noonan syndromes and congenital lymphatic malformations. Traumatic causes include injury to the thoracic duct during surgical repairs of diaphragmatic hernias, tracheoesophageal fistulas, and congenital heart disease repair, or injury during the birthing process. Nontraumatic forms of chylothorax are extremely rare in the neonatal period. Other forms of exudative effusions include extravasation of parenteral nutrition, infectious, and inflammatory disorders. *Acinetobacter calcoaceticus*, *Staphylococcus* species, *Streptococcus pneumoniae,* group B *Streptococcus* species, and *Bacteroides fragilis* have all been described in the literature as causing parapneumonic effusions.

Transudative effusions, in comparison, are classically a result of increased hydrostatic pressure (ie, congestive heart failure and fetal hydrops) or impaired lymphatic drainage (ie, subtypes of pulmonary lymphatic malformations). Other potential etiologies include congenital heart disease with elevated pulmonary venous pressures, hypoproteinemia, renal failure, elevated central venous pressures (as seen in superior vena cava thromboses) with subsequent impairment of lymphatic drainage, and extravasation of colloidal fluid from a central venous line.

Hydrops fetalis typically presents prenatally with 2 or more of the following: ascites, pleural effusions, pericardial effusions, or skin edema. Hydrops is associated with anemia, congenital anomalies, chromosomal abnormalities, infections, and twin-twin transfusion syndrome. Unlike other causes of pleural effusions in the neonate, diagnosis of hydrops carries a much greater mortality rate, greater than 50% in some reports.

Regardless of the cause, acute management of symptomatic effusions includes resuscitation with intubation and mechanical ventilation if indicated. After initial stabilization, thoracentesis should be performed for both symptomatic relief and further diagnostic evaluation. Drainage of the fluid typically results in lung expansion and improvement in respiratory distress. As noted previously herein, evaluation of the fluid includes extensive laboratory testing. In addition to the studies mentioned previously herein, fluid should be sent for Gram-stain and culture. Impairments in lymphatic drainage and, more specifically, a chylothorax may demand medical management if the patient is either too unstable to undergo thoracentesis or if fluid reaccumulates after thoracentesis. Medical management includes the use of specialty formulas with higher medium-chain triglyceride content. The mechanism of action is reduction of intestinal lymph production, thereby decreasing flow through the thoracic duct. In addition, for those instances that do not resolve after drainage or specialty formula, octreotide, a somatostatin analog, may play a role in reducing the need for surgical intervention and decrease length of hospitalization.

Prognosis of pleural effusions depends on the specific etiology. As a general rule, fetal pleural effusions (presumably due to associated conditions and potential for pulmonary hypoplasia), effusions as a part of hydrops fetalis presentation, and bilateral effusions carry greater morbidity and mortality. A basic understanding of common etiologies and a standardized approach to patients with pleural effusions allows for prompt diagnosis and treatment.

PATIENT COURSE

This neonate was evaluated with chest radiography, echocardiography, chest and abdominal ultrasonography, and thoracentesis (Figs 1 and 2). Abdominal ultrasonography demonstrated the correct placement of the UVC tip in the inferior vena cava; despite the appropriate position, the UVC was removed. The echocardiogram revealed a pericardial effusion, normal cardiac architecture, and no evidence of diastolic dysfunction. The patient never developed signs of cardiac tamponade. After thoracentesis the patient improved within minutes; she had decreased tachypnea and less labored breathing. Overall, the patient did well and did not have recurrence of the pleural effusion after removal of the UVC and thoracentesis. Repeated echocardiography 2 weeks after the initial decompensation demonstrated near complete resolution of the pericardial effusion.

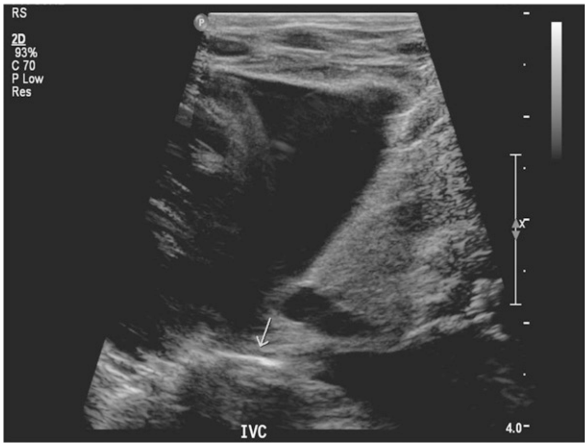

Figure 2. Ultrasonographic image demonstrating the tip of the umbilical venous catheter in the inferior vena cava, moderate-sized pericardial effusion, and moderate-sized pleural effusions.

Summary

- There is an extensive differential diagnosis for pleural effusions in the neonatal period, but common etiologies include chylothorax and complications of central catheters.
- In patients who develop pleural effusion after placement of a central catheter, the catheter should be removed even if it is shown to be in proper position.
- Evaluation of pleural effusion consists of imaging and laboratory studies. Treatment is based on the specific etiology; however, acute management includes stabilization of respiratory distress and thoracentesis.
- Increased mortality from pleural effusion is associated with fetal effusions, bilateral effusions, and hydrops fetalis.

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Air Force, the Department of the Army, the Department of Defense, or the US Government.

Suggested Readings

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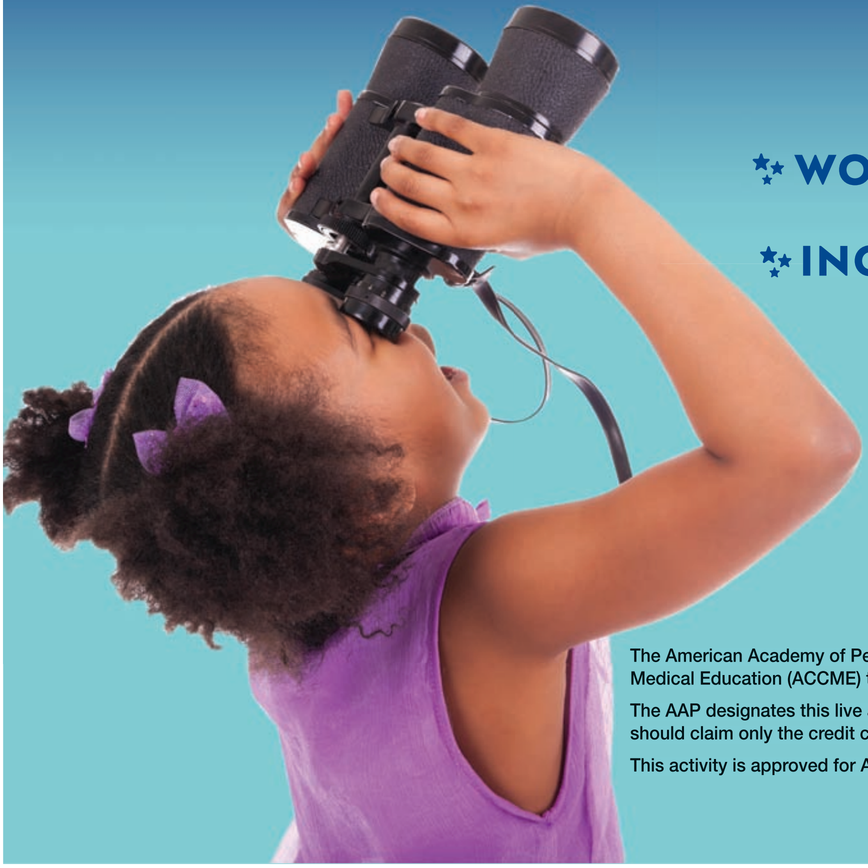

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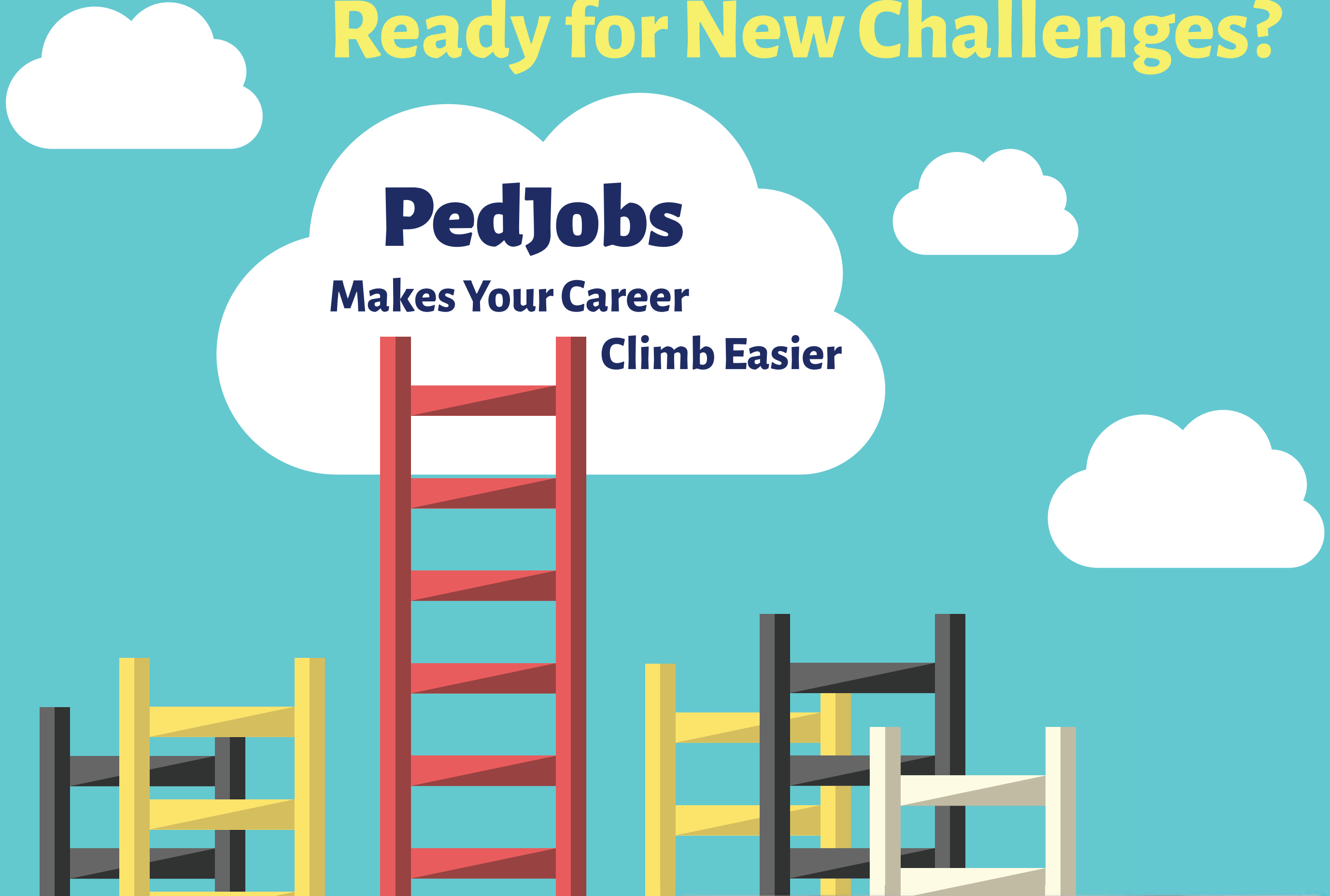

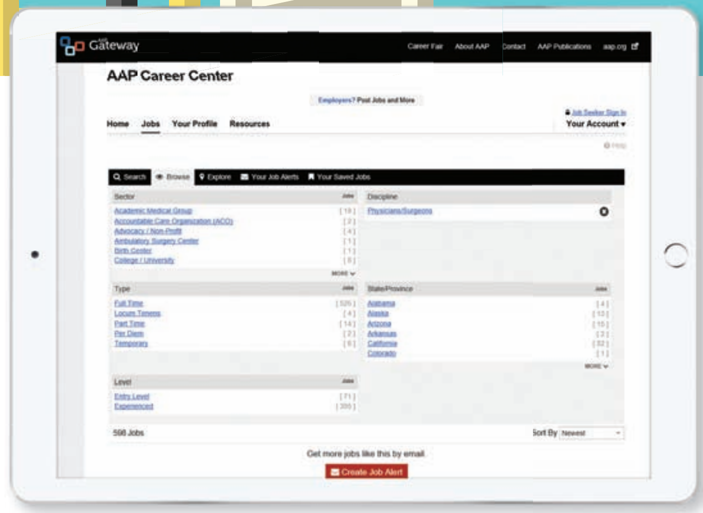

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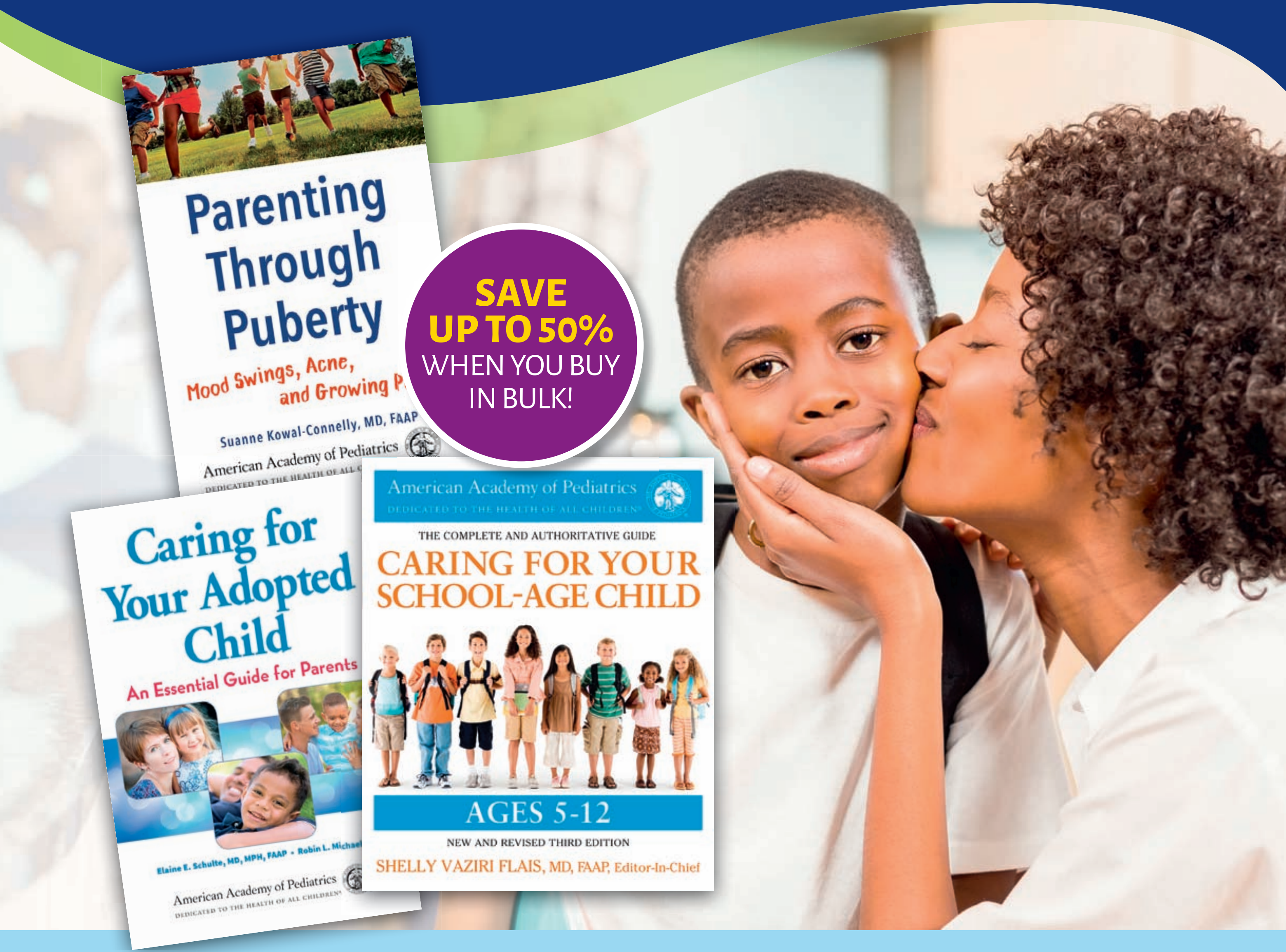
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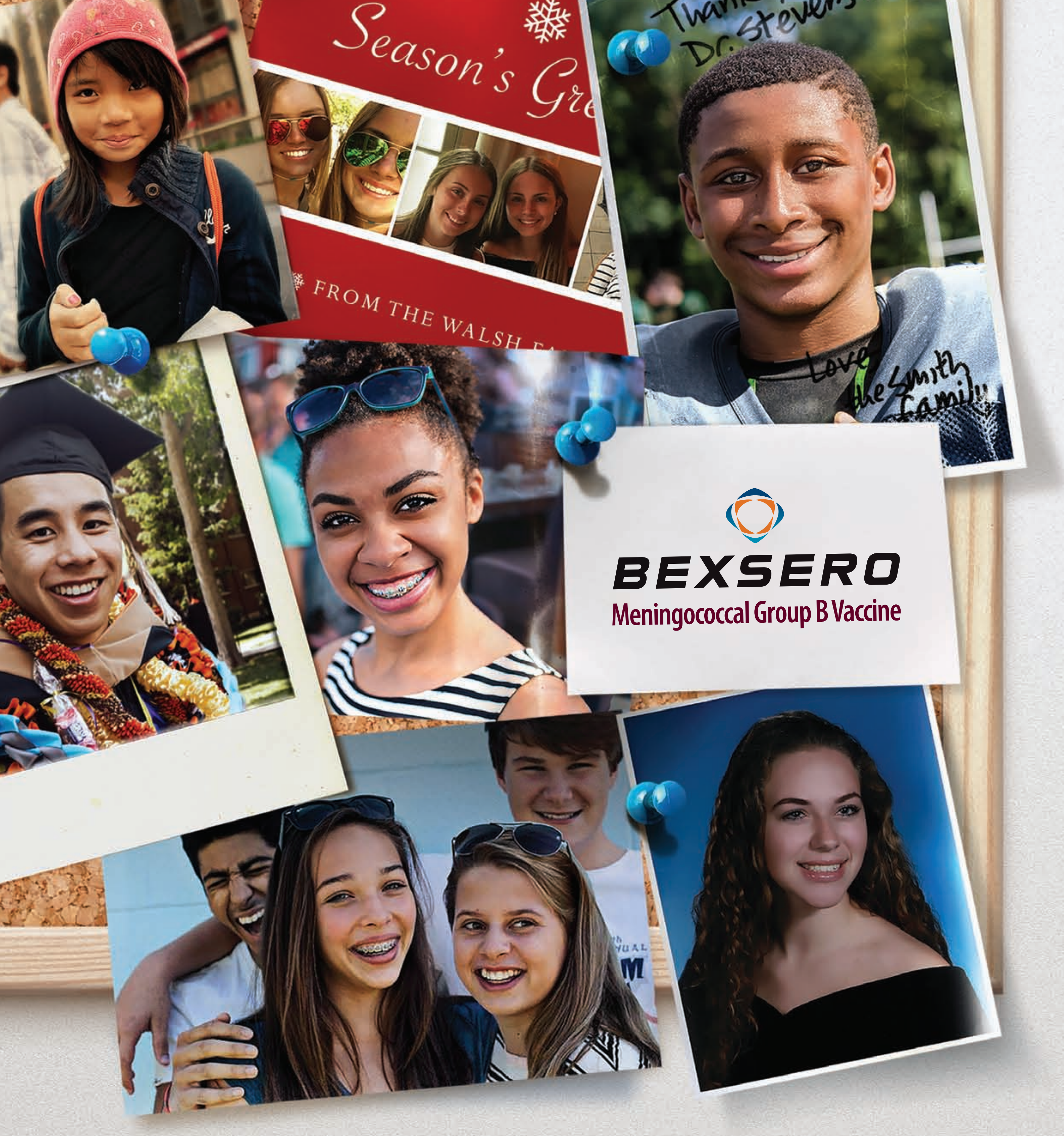

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Indication for BEXSERO

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

Important Safety Information for BEXSERO

- BEXSERO is contraindicated in cases of hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO
- Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine
- The tip caps of the prefilled syringes contain natural rubber latex, which may cause allergic reactions in latex-sensitive individuals
- Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope
- The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%)
- Vaccination with BEXSERO may not provide protection against all meningococcal serogroup B strains
- Some individuals with altered immunocompetence may have reduced immune responses to BEXSERO
- Vaccination with BEXSERO may not result in protection in all vaccine recipients

Please see accompanying brief summary of full Prescribing Information for BEXSERO.

References: 1. Prescribing Information for BEXSERO. **2.** Prescribing Information for TRUMENBA..

BRIEF SUMMARY

BEXSERO (Meningococcal Group B Vaccine)
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The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. BEXSERO is approved for use in individuals 10 through 25 years of age.

Approval of BEXSERO is based on demonstration of immune response, as measured by serum bactericidal activity against three serogroup B strains representative of prevalent strains in the United States. The effectiveness of BEXSERO against diverse serogroup B strains has not been confirmed.

4 CONTRAINDICATIONS

Hypersensitivity, including severe allergic reaction, to any component of the vaccine, or after a previous dose of BEXSERO. *[see Description (11) of full prescribing information].*

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Reactions

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the vaccine.

5.2 Syncope

Syncope (fainting) can occur in association with administration of BEXSERO. Ensure procedures are in place to avoid injury from falling associated with syncope.

5.3 Latex

The tip caps of the pre-filled syringes contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitation of Vaccine Effectiveness

BEXSERO may not protect all vaccine recipients. BEXSERO may not provide protection against all meningococcal serogroup B strains *[see Clinical Pharmacology (12.1) of full prescribing information].*

5.5 Altered Immunocompetence

Some Individuals with altered immunocompetence may have reduced immune responses to BEXSERO.

Complement Deficiency

Persons with certain complement deficiencies and persons receiving treatment that inhibits terminal complement activation (for example, eculizumab) are at increased risk for invasive disease caused by *N. meningitidis* serogroup B even if they develop antibodies following vaccination with BEXSERO. *[See Clinical Pharmacology (12.1).]*

6 ADVERSE REACTIONS

The most common solicited adverse reactions observed in clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In 4 clinical trials, 3058 individuals aged 10 through 25 years of age received at least one dose of BEXSERO, 1436 participants received only BEXSERO, 2089 received only placebo or a control vaccine, and 1622 participants received a mixed regimen (placebo or control vaccine and BEXSERO).

In a randomized controlled study[1] conducted in US and Poland, 120 participants aged 10 through 25 years of age received at least one dose of BEXSERO, including 112 participants who received 2 doses of BEXSERO 2 months apart; 97 participants received saline placebo followed by MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM$_{197}$ Conjugate Vaccine]. Across groups, median age was 13 years, males comprised 49% and 60% were White; 34% were Hispanic, 4% were Black,<1% were Asian, and 2% were other.

In a second randomized controlled study[2] conducted in Chile, all subjects (N=1,622) aged 11 through 17 years of age received at least 1 dose of BEXSERO. This study included a subset of 810 subjects who received 2 doses of BEXSERO 1 or 2 months apart. A control group of 128 subjects received at least 1 dose of placebo containing aluminum hydroxide. A subgroup of 128 subjects received 2 doses of BEXSERO 6 months apart. In this study, median age was 14 years, males comprised 44%, and 99% were Hispanic.

In a third randomized controlled study[3] conducted in the United Kingdom (UK), 974 university students aged 18 through 24 years of age received at least 1 dose of BEXSERO, including 932 subjects who received 2 doses of BEXSERO 1 month apart. Comparator groups received 1 dose of MENVEO followed by 1 dose of placebo containing aluminum hydroxide (n=956) or 2 doses of IXIARO (Japanese Encephalitis Vaccine, Inactivated, Adsorbed) (n=947). Across groups, median age was 20 years, males comprised 46%, and 88% were White, 5% were Asian, 2% were Black, <1% were Hispanic, and 4% were other.

In an uncontrolled study[4] conducted in Canada and Australia, 342 participants aged 11 through 17 years of age received at least 1 dose of BEXSERO, including 338 participants who received 2 doses of BEXSERO 1 month apart. The median age was 13 years, males comprised 55%, and 80% were White, 10% were Asian, 4% were Native American/Alaskan, and 4% were other.

Local and systemic reactogenicity data were solicited from all participants in the studies conducted in Chile, US/Poland, Canada/Australia, and in a subset of participants in the UK study. Reports of unsolicited adverse events occurring within the first 7 days after each vaccination were collected in all studies. In the US/Poland study, reports of unsolicited adverse events were collected up to one month after the second vaccination.

Reports of all serious adverse events, medically attended adverse events and adverse events leading to premature withdrawal were collected throughout the study period for the studies conducted in Chile (12 months), UK (12 months), US/Poland (8 months), and Canada/Australia (2 months).

Solicited Adverse Reactions

The reported rates of local and systemic reactions among participants 10 through 25 years of age following each dose of BEXSERO administered 2 months apart or control in the US/Polish study[1] are presented in Table 1 and Table 2.

Table 1: Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Local Solicited Adverse Reactions[a] within 7 Days after BEXSERO or Control, by Dose

Local Adverse Reaction		Dose 1 BEXSERO n = 110-114	Dose 1 Placebo (Saline) n = 94-96	Dose 2[b] BEXSERO n = 107-109	Dose 2[b] MENVEO n = 90-92
Pain	Any	90	27	83	43
	Mild	27	20	18	26
	Moderate	44	5	37	9
	Severe	20	2	29	8
Erythema	Any	50	13	45	26
	1-25 mm	41	11	36	13
	>25-50 mm	6	1	5	6
	>50-100 mm	3	0	5	4
	>100 mm	0	0	0	2
Induration	Any	32	10	28	23
	1-25 mm	24	9	22	16
	>25-50 mm	7	0	4	0
	>50-100 mm	1	1	2	4
	>100 mm	0	0	0	2

Clinicaltrials.gov Identifier NCT01272180.

[a] Erythema and induration: Any (≥1 mm). Pain: Mild (transient with no limitation in normal daily activity); Moderate (some limitation in normal daily activity); Severe (unable to perform normal daily activity).

[b] Administered 2 months after Dose 1.

Table 2. Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Systemic Adverse Reactions[a] within 7 Days after BEXSERO or Control, by Dose

Systemic Adverse Reaction		Dose 1 BEXSERO n = 110-114	Dose 1 Placebo (Saline) n = 94-96	Dose 2[b] BEXSERO n = 107-109	Dose 2[b] MENVEO n = 90-92
Fatigue	Any	37	22	35	20
	Mild	19	17	18	11
	Moderate	14	5	10	7
	Severe	4	0	6	2
Nausea	Any	19	4	18	4
	Mild	12	3	10	3
	Moderate	4	1	5	1
	Severe	4	0	4	0
Myalgia	Any	49	26	48	25
	Mild	21	20	16	14
	Moderate	16	5	19	7
	Severe	12	1	13	4
Arthralgia	Any	13	4	16	4
	Mild	9	3	8	2
	Moderate	3	1	6	2
	Severe	2	0	2	0
Headache	Any	33	20	34	23
	Mild	19	15	21	8
	Moderate	9	4	6	12
	Severe	4	1	6	3
Fever	≥38°C	1	1	5	0
	38.0-38.9°C	1	1	4	0
	39.0-39.9°C	0	0	1	0
	≥40°C	0	0	0	0

(continued on next page)

Table 2. Percentage of U.S. and Polish Participants Aged 10 through 25 Years Reporting Systemic Adverse Reactions[a] within 7 Days after BEXSERO or Control, by Dose *(cont'd)*

Clinicaltrials.gov Identifier NCT01272180.

[a] Systemic reactions: Mild (transient with no limitation in normal daily activity); Moderate (some limitation in normal daily activity); Severe (unable to perform normal daily activity).

[b] Administered 2 months after Dose 1.

Solicited adverse reaction rates were similar among participants 11 through 24 years of age who received BEXSERO in the other three clinical studies,[2,3,4] except for severe myalgia which was reported by 3-7% of subjects. Severe pain was reported by 8% of university students in the UK[3].

Non-serious Adverse Events

In the 3 controlled studies[1,2,3] (BEXSERO n=2221, control n=2204), non-serious unsolicited adverse events that occurred within 7 days of any dose were reported by 439 (20%) receiving BEXSERO and 197 (9%) control recipients. Unsolicited adverse events that were reported among at least 2% of participants and were more frequently reported in participants receiving BEXSERO than in control recipients were injection site pain, headache, and injection site induration unresolved within 7 days, and nasopharyngitis.

Serious Adverse Events

Overall, in clinical studies, among 3,058 participants aged 10 through 25 years of age who received at least 1 dose of BEXSERO, 66 (2.1%) participants reported serious adverse events at any time during the study. In the 3 controlled studies[1,2,3] (BEXSERO n=2716, Control n=2078), serious adverse events within 30 days after any dose were reported in 23 (0.8%) participants receiving BEXSERO and 10 (0.5%) control recipients.

6.2 Additional Pre-licensure Safety Experience

In response to outbreaks of serogroup B meningococcal disease at 2 universities in the US, BEXSERO was administered as a 2-dose series at least 1 month apart. Information on serious adverse events was collected for a period of 30 days after each dose from 15,351 individuals aged 16 through 65 years of age who received at least 1 dose. Overall 50 individuals (0.3%) reported serious adverse events, including one event considered related to vaccination, a case of anaphylaxis within 30 minutes following vaccination.

6.3 Postmarketing Experience

Adverse event reports received for BEXSERO marketed outside the US are listed below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency, or to establish a causal relationship to vaccination. This list includes serious events or events which have suspected causal association to BEXSERO.

General Disorders and Administration Site Conditions:	Injection site reactions (including extensive swelling of the vaccinated limb, blisters at or around the injection site, and injection site nodule which may persist for more than 1 month).
Immune System Disorders:	Allergic reactions (including anaphylactic reactions), rash, eye swelling.
Nervous System Disorders:	Syncope, vasovagal responses to injection.

7 DRUG INTERACTIONS

Sufficient data are not available to establish the safety and immunogenicity of concomitant administration of BEXSERO with recommended adolescent vaccines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility in females or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Pregnancy Registry for BEXSERO

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following exposure to BEXSERO during pregnancy. Women who receive BEXSERO during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-877-413-4759.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of BEXSERO have not been established in children younger than 10 years of age.

8.5 Geriatric Use

Safety and effectiveness of BEXSERO have not been established in adults older than 65 years of age.

15 REFERENCES

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17 PATIENT COUNSELING INFORMATION

S*ee FDA-Approved Patient Labeling.*

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Pediatric Cervical Lymphadenopathy

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Practice Gaps

Pediatric cervical lymphadenopathy is a common disease entity, with multiple processes ranging from benign and self-resolving to malignant. The changing use of imaging modalities, including ultrasonography, computed tomography, and magnetic resonance imaging, continues to alter the recommended diagnostic evaluation. This review provides a general outline of the differential diagnosis for cervical lymphadenopathy, with updates on the current data regarding imaging and biopsy modalities to guide practitioners on when lymphadenopathy is concerning enough to warrant further evaluation, and what that evaluation should entail.

Objectives

After completing this article, readers should be able to:

1. Understand basic anatomical considerations when evaluating the pediatric population for cervical lymphadenopathy.
2. Develop a broad differential diagnosis, including the most common and most life-threatening causes of cervical lymphadenopathy.
3. Determine a reasonable diagnostic pathway for patients who present with acute, subacute, and chronic lymphadenopathy.
4. Initiate treatment for certain conditions when appropriate.

Abstract

Cervical lymphadenopathy affects as many as 90% of children aged 4 to 8 years. With so many children presenting to doctors' offices and emergency departments, a systematic approach to diagnosis and evaluation must be considered. In the following review, we aim to provide the pediatric clinician with a general framework for an appropriate history and physical examination, while giving guidance on initial diagnostic laboratory testing, imaging, and potential need for biopsy. The most common cause of cervical lymphadenopathy in the pediatric population is reactivity to known and unknown viral agents. The second most common cause includes bacterial infections ranging from aerobic to anaerobic to mycobacterial infections. Malignancies are the most concerning cause of cervical lymphadenopathy.

AUTHOR DISCLOSURE Drs Weinstock, Patel, and Smith have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

CMV	cytomegalovirus
CT	computed tomography
EBV	Epstein-Barr virus
FNA	fine-needle aspiration
HIV	human immunodeficiency virus
MRI	magnetic resonance imaging

The explosion in the use of ultrasonography as a nonradiating imaging modality in the pediatric population has changed the diagnostic algorithm for many clinicians. We aim to provide some clarity on the utility and shortcomings of the imaging modalities available, including ultrasonography, computed tomography, and magnetic resonance imaging.

INTRODUCTION

Cervical lymphadenopathy is a strikingly common occurrence; estimates vary, but the incidence of lymphadenopathy in the pediatric population ranges from 62% in patients aged 3 weeks to 6 months to 41% in those 2 to 5 years old (1) to upwards of 90% of all children 4 to 8 years old. (2) A study by Larsson et al (3) estimated that approximately 40% of healthy children have palpable lymphadenopathy. Nearly every pediatric physician will encounter scores of patients with lymphadenopathy—in this article, we aim to provide practitioners with a review of the diagnostic and treatment modalities available.

HISTORY AND PHYSICAL EXAMINATION

The most powerful, most cost-effective, and least invasive diagnostic tool available is the history and physical examination. Several questions will direct the differential diagnosis: 1) What is the duration of the lymphadenopathy? 2) Does the size fluctuate? 3) Are there any concerning associated symptoms, including fever, weight loss, night sweats, easy bruisability, fatigue? 4) Has the patient attempted a treatment of any type yet? If so, which antibiotics, etc? 5) Does the patient have any recent animal (eg, cats) or travel exposures?

The physical examination should focus on the lymph chains of the head and neck. In general, they are divided into submental, submandibular, parotid, anterior cervical, posterior cervical, and supraclavicular chains. The size and location of the lymph node and whether located unilaterally or bilaterally will direct the differential diagnosis, as well as the quality of the lymph node. Is it firm or matted, rubbery or soft, fluctuant/ballotable, mobile or immobile, tender to palpation, warm, and/or erythematous? Are there overlying skin changes? The range of motion of the neck should also be noted. In terms of location, palpable supraclavicular nodes are the most likely to be malignant and should always be investigated. Posterior cervical lymph nodes drain the scalp and raise the differential diagnosis for mononucleosis. Submandibular lymphadenopathy is more likely to suggest mononucleosis or atypical mycobacterium. (4)

DIFFERENTIAL DIAGNOSIS

Several key components exist in making the diagnosis of a patient who presents with cervical lymphadenopathy. It may be helpful to couch the discussion in terms of 1) what is most likely/most common, 2) what is most dangerous, and 3) what further diagnostic steps, if any, one should take to make a diagnosis. For a more complete list of the differential diagnosis of cervical lymphadenopathy, refer to the Table.

REACTIVE CERVICAL LYMPHADENOPATHY SECONDARY TO VIRAL INFECTION

The most common cause of cervical lymphadenopathy in the pediatric population is lymphadenopathy secondary to a viral infection. Because of lymphadenopathy's inflammatory nature, it could also be termed *lymphadenitis*. Typically, patients will have a history of a viral prodrome. The reactive lymph node(s) may be tender to palpation and have a unilateral or bilateral location. Most importantly, the lymphadenopathy typically resolves with resolution of the viral illness. Common viruses, including rhinovirus, adenovirus, influenza, parainfluenza, and respiratory syncytial virus, may induce a self-resolving and uncomplicated cervical lymphadenopathy.

Some other viral causes of cervical lymphadenopathy may present in an acute (<3 weeks), subacute (3–6 weeks), or chronic (>6 weeks) manner. These causes include Epstein-Barr virus (EBV), causing mononucleosis, and cytomegalovirus (CMV), as well as human immunodeficiency virus (HIV). Often, EBV and CMV present in a similar manner, with both producing acute to subacute periods of fatigue, fever, and tender, bilateral, often posterior cervical lymphadenopathy. Often, EBV produces pharyngitis and a sore throat, whereas CMV rarely does. When patients have several of these symptoms, a monospot test, with or without EBV antibody titers and CMV serologic assay, may be warranted to help with the diagnostic evaluation.

TABLE. **Causes of Pediatric Cervical Lymphadenopathy**

o Infectious
■ Reactive to viral antigens
• Acute: Rhinovirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus, others
■ Subacute or chronic: Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus bacterial
• Acute: *Staphylococcus aureus*, group A streptococcus
• Neonates: Group B streptococcus
• Rarely: Anaerobes
• Subacute or chronic: *Bartonella*
■ Atypical mycobacterial and *Mycobacterium tuberculosis*
■ Fungal
■ Parasites
o Congenital neck mass
■ Thyroglossal duct cyst, dermoid, branchial cleft, lymphovascular malformation, hemangioma, ectopic thymus
o Malignancies
■ Lymphoma
■ Rhabdosarcoma
■ Neuroblastoma
o Metastasis (especially from nasopharyngeal and thyroid cancer)
o Miscellaneous
■ Kikuchi-Fujimoto disease
■ Rosai-Dorfman disease
■ Langerhans cell histiocytosis
■ Kawasaki disease
■ Castleman disease

HIV may also cause subacute/chronic reactive lymphadenopathy in the pediatric population. This will often be accompanied by a constellation of symptoms, including fever and fatigue, as well as a potential source for the infection.

Viral lymphadenopathy, in general, will require supportive care only. However, viral lymphadenopathy may develop into suppurative or bacterial lymphadenopathy over time.

ACUTE BACTERIAL LYMPHADENITIS/SUPPURATIVE LYMPHADENITIS

The second most common cause of lymphadenopathy in the pediatric population is secondary to a bacterial infection and could be termed *lymphadenitis*. The pathogens most commonly isolated include *Staphylococcus aureus* and group B streptococcus (in neonates), group A streptococcus, and anaerobic infections. (5)(6) The history and physical examination findings may point the clinician toward a diagnosis of acute bacterial lymphadenitis. In general, the timing of onset will be days to perhaps a week of fever with an enlarging neck swelling. On physical examination, the neck range of motion may be limited. Neck swelling may be firm and/or tender, with or without overlying erythema.

Approximately 25% of patients with an abscess will be noted to have fluctuance on physical examination. (7) Induration and immobility of the neck mass may also be present; if these findings are present over a longer time course, the clinician should also be concerned about possible malignancy. When differentiating between viral and bacterial lymphadenitis, it is important to remember that viral lymphadenitis self-resolves. If the patient does not begin to show resolution of infection within 4 to 7 days, the clinician should become concerned about the presence of either a primary bacterial lymphadenitis or a viral lymphadenitis that has become infected with bacteria.

The treatment for suspected bacterial cervical lymphadenitis starts with appropriate antibiotic coverage. Patients may begin oral treatment with agents that cover for the most common pathogens (*S aureus*, *Streptococcus pyogenes*, anaerobic pathogens). This may include clindamycin, amoxicillin/clavulanate, or macrolides. If patients require intravenous antibiotics, the typical regimen starts with clindamycin or ampicillin/sulbactam. A combination of vancomycin and ceftriaxone can be used if the initial empirical regimen is insufficient. A recent analysis of incision and drainage of acute suppurative bacterial cervical lymphadenitis revealed that more than 54% of pathogens isolated were *S aureus* or *S pyogenes* (35.7% and 18.8%, respectively). Only 1% of isolates revealed anaerobes, and 2% revealed acid-fast bacilli. (8)

Antibiotics alone may be able to treat many bacterial infections that result in cervical lymphadenitis. Large fluctuant or persistent cervical lymphadenitis that does not respond within 48 to 72 hours with systemic signs of infection should alert the clinician to the possibility of abscess formation. Clinicians may first consider ultrasonography to evaluate for abscess formation. The specificity and sensitivity of ultrasonography for detecting abscess formation is user dependent and variable. However, the downside of a brief noninvasive examination with no radiation exposure is minimal. If equivocal, or if the lymphadenitis is highly suspicious for abscess formation or present in an anatomical area requiring more detailed information (eg, deep to the sternocleidomastoid muscle), a computed tomographic (CT) scan or magnetic resonance image (MRI) with intravenous contrast will give more detailed information. This is especially valuable if the differential diagnosis includes an infected branchial cleft anomaly or lymphatic malformation (Figs 1 and 2).

An abscess smaller than 1 × 1 × 1 cm may not require surgical drainage. Some children with abscesses approximating 1.5 cm may also resolve on their own with a trial of antibiotics. Clinicians may consider a trial of 24 to 48 hours of intravenous antibiotics before incision and drainage for abscesses less than 1.5 to 2 cm if the child is clinically stable. If the location of the abscess is anatomically difficult, or if the abscess is small but persistent, image-guided needle aspiration with or without drain placement may be appropriate, although recurrence rates are likely higher for needle drainage versus incision and drainage. Cultures should be taken to help direct the antibiotic regimen.

SUBACUTE OR CHRONIC LYMPHADENOPATHY

When patients have an infectious process causing cervical lymphadenopathy occurring for 2 to 6 weeks it is considered a subacute infection; when that process occurs for more than 6 weeks it is considered chronic. Possible causes of these infections include a *Bartonella* infection causing cat-scratch disease, toxoplasmosis, viral infections (eg, CMV, HIV), and mycobacterial infections. Of course, with prolonged lymphadenopathy, the possibility of a malignancy needs to be considered. Clinicians should never assume that all enlarged cervical lymph nodes are infectious in etiology.

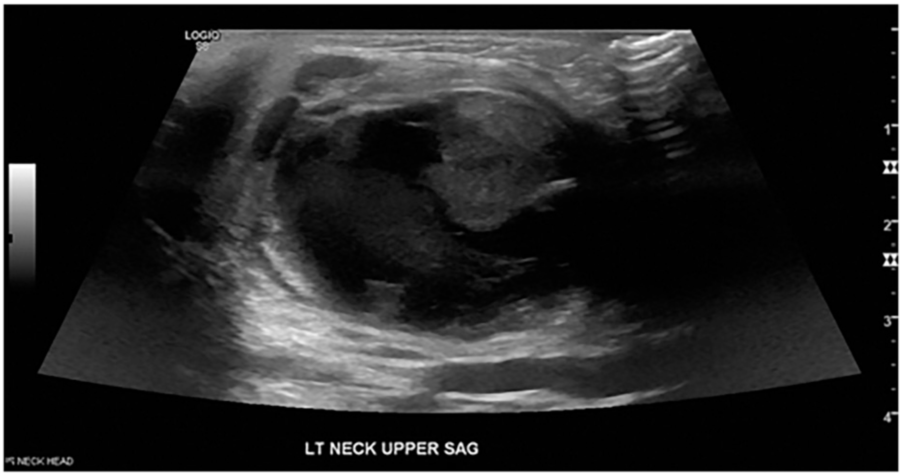


Figure 1. A 20-month-old girl presents with fever and tender lymphadenopathy. Ultrasonography shows a large complex collection measuring 4.0 × 2.6 × 3.0 cm, consistent with a suppurative lymph node.

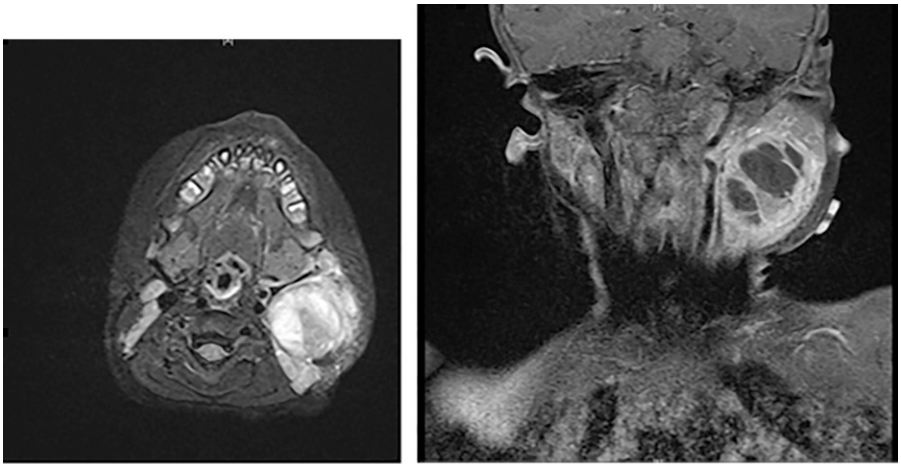


Figure 2. A 20-month-old girl presents with a large lateral neck collection. T2-weighted axial and coronal magnetic resonance images show a 3.9 × 2.7 × 3.0-cm multiloculated neck abscess.

Bartonella henselae causes a granulomatous infection, usually transmitted by the scratch or bite of a cat. It results in lymphadenopathy that may occur either immediately or several weeks after the injury. Many patients will have spontaneous resolution of symptoms without any antibiotics. The first line of antibiotic treatment is azithromycin; however, clarithromycin, ciprofloxacin, or sulfamethoxazole/trimethoprim may be considered. If the patient does not improve with antibiotic therapy, surgical excision of the infected material can be undertaken. (9)

Atypical mycobacterial infections cause indolent, chronic cervical lymphadenopathy, usually present in the submandibular region of the neck. Children are often afebrile, and nodes are classically enlarged, nontender, indurated, and possibly fluctuant. Often there is an overlying violaceous discoloration of the skin (Fig 3). Purified protein derivative skin testing may be weakly positive but will be negative in many cases of atypical mycobacterial infections. If an atypical mycobacterial infection is suspected, diagnosis may be confirmed with fine-needle aspiration (FNA). Treatment options are variable and controversial and range from medical therapy or surgical therapy alone to a combination of the two. Surgical treatment would usually involve complete excision of the involved lymph node. Incision and drainage should be avoided because this may result in a chronically draining fistula. Complete surgical excision results in a cure rate of more than 95% compared with medical therapy with a cure rate of only 66%. (10) If the involved lymph node cannot be safely excised (for instance due to the proximity of the facial nerve), surgeons can consider curettage of the affected tissue with observation and medical management (often with dual therapy of clarithromycin and rifampin).

Scrofula, or *Mycobacterium tuberculosis*, may also be a cause of chronic cervical lymphadenopathy. Purified protein derivative skin testing and QuantiFERON-TB Gold® (Qiagen, Valencia, CA) testing can be used make the diagnosis; FNA of the lymph node may also be attempted to confirm the diagnosis. When in doubt, excisional biopsy of the node in question may be required. If positive, treatment will typically involve medical management. Although they may occur anywhere, these lesions are classically supraclavicular in location. Again, an incision and drainage procedure may result in a chronically draining fistula. Fine-needle aspirate may also be helpful for diagnosis.

Chronic infectious lymphadenopathy may also be caused by parasitic infections, the most common of which is toxoplasmosis. A common protozoan in cat feces and raw pork, *Toxoplasma gondii* may present with nontender, nonsuppurative lymphadenopathy. If toxoplasma infection is

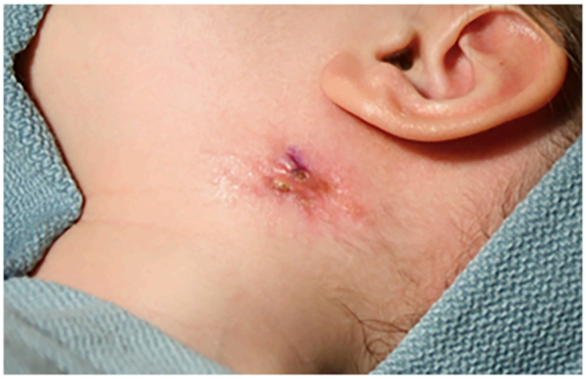


Figure 3. A 4-year-old girl with an atypical mycobacterial infection. The overlying skin is violaceous and indurated.

suspected, polymerase chain reaction may be used to analyze blood samples for diagnostic purposes. It is treated with a combination of pyrimethamine, sulfadiazine, and leucovorin initially. The infection typically resolves in 4 to 6 weeks. (11)

NONINFECTIOUS CAUSES OF CERVICAL LYMPHADENOPATHY IN CHILDREN

Although most cases of cervical lymphadenopathy in the pediatric population are caused by infectious processes, cervical lymphadenopathy may be caused by other processes that can be confused with infectious cervical lymphadenopathy and are worth mentioning in this review.

MALIGNANCY

Patients with persistent cervical lymphadenopathy may present with either primary or metastatic malignancy. Before age 6 years, the most common malignancies are rhabdomyosarcoma and non-Hodgkin's lymphoma. After age 6 years, the most common malignancy is Hodgkin lymphoma. (12) A history of night sweats, fatigue, fever, easy bleeding or bruising, and/or weight loss may point the clinician toward a possible malignant diagnosis. More common (although still very rare) metastatic disease to the neck in the pediatric population includes papillary thyroid cancer and nasopharyngeal cancer. Physical examination characteristics concerning for malignancy include firm, indurated masses that are matted down and often nontender to palpation. Bilateral nodes are less concerning than unilateral lymph nodes; in a recent study, none of the patients with bilateral nodes had concerning pathology, whereas up to 20% of patients with unilateral lymphadenopathy had concerning pathology. (13) However, unilaterality cannot necessarily be used as a reliable predictor of pathology. Niedzielska et al (14) found that up to 70% of patients with reactive nodal changes only had unilateral disease (Fig 4).

CONGENITAL NECK MASSES

Congenital neck mass may be confused for lymphadenopathy. Midline neck masses are often not lymph nodes. These lesions are usually either thyroglossal duct cysts or dermoid cysts. Ultrasonography can be helpful to characterize these lesions and differentiate them from lymphadenopathy. Most dermoid and thyroglossal duct cysts should be treated with surgical excision. Preoperative ultrasonography to confirm the presence of a normal orthotopic thyroid gland should be performed before excision of a thyroglossal duct cyst to ensure that the thyroglossal duct cyst does not represent an ectopic thyroid gland.

In the lateral neck, second branchial cleft cysts may present as a swelling deep to the sternocleidomastoid muscle that can be confused for lymphadenopathy. Screening ultrasonography may be performed. Computed tomography or MRI is usually diagnostic. If there is uncertainty, FNA may be performed. Most second branchial cleft cysts are treated with complete surgical excision.

Third branchial anomalies (or pyriform sinus anomalies) will usually present just off midline in the region of the thyroid gland, most often posterior to the left lobe of the thyroid gland. Computed tomography or MRI is usually diagnostic in these cases, and treatment usually requires surgery, during which time the surgeon may use an endoscopic technique to cauterize the pyriform sinus outflow tract. (15)

An ectopic thymus can also present as a lateral neck mass. Ultrasonography is usually diagnostic and avoids unnecessary surgery. An FNA can be performed if the diagnosis is still in question.

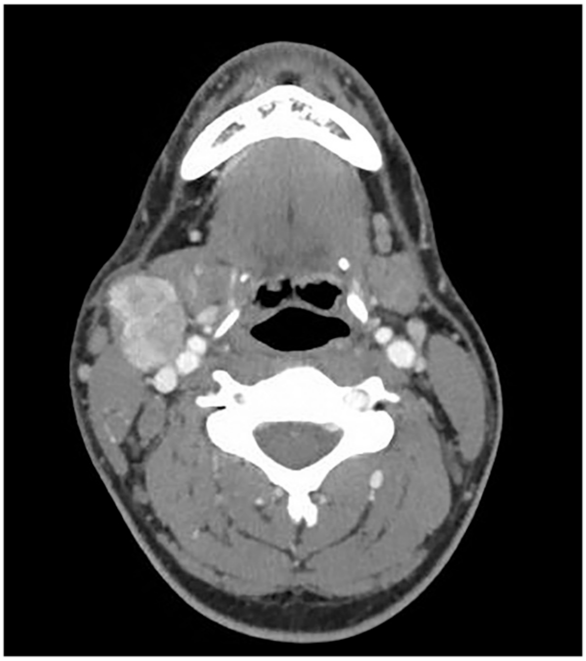


Figure 4. Axial cut of a computed tomographic scan with contrast of an 8-year-old girl with papillary thyroid carcinoma. The 3 × 4-cm lymph node superficial to the great vessels in the right neck represents a regional metastasis of the disease.

NONINFECTIOUS CAUSES

Several disease processes that are not congenital, infectious, or malignant may cause cervical lymphadenopathy. Kikuchi-Fujimoto disease (or histiocytic necrotizing lymphadenitis) is a benign, self-limited disease characterized by tender cervical lymphadenopathy with night sweats as well as general malaise and sore throat, nausea, and vomiting. The diagnosis is usually made by incisional or excisional biopsy. It is a self-resolving disease, with complete resolution of symptoms in 1 to 3 months. (16) The onset of symptoms is typically in the subacute range, with approximately 2 to 4 weeks of cervical tenderness, and the disease is most frequently found in young Japanese women.

Rosai-Dorfman disease, also known as non–Langerhans cell histiocytosis, and Langerhans cell histiocytosis are lymphoproliferative disorders that can also affect children. Patients with Rosai-Dorfman disease classically present with bilateral painless lymphadenopathy, fever, and abnormal laboratory findings including an elevated erythrocyte sedimentation rate. (17) These lesions require biopsy to confirm the diagnosis. Langerhans cell histiocytosis is characterized by an accumulation of Langerhans cells in the lymph nodes, with a diagnosis made on biopsy. (18)

Kawasaki disease may also present with tender cervical lymphadenopathy, as this is 1 of the 5 major findings required to diagnose Kawasaki disease, the other criteria including edema and peeling of the extremities, polymorphous exanthem, conjunctival injection, lip cracking, and strawberry tongue, in addition to fever for more than 5 days. (19)

Castleman disease is another rare lymphoproliferative disorder that can present with tender cervical lymphadenopathy. Patients often experience fever, night sweats, fatigue, and cachexia with 2 to 4 weeks of subacute cervical lymphadenopathy. The disease is characterized by excessive growth of B lymphocytes and plasma cells. It typically resolves on its own, although new immunotherapies have also helped in refractory cases. (20)

PAROTID, SUBMANDIBULAR, AND SUBLINGUAL GLAND PATHOLOGY

Salivary gland pathology may also be confused with cervical lymphadenopathy. The tail of the parotid gland dips posterior and sometimes inferior to the angle of the mandible, which may confuse the location with cervical lymph nodes located in the upper jugular area of the neck. The submandibular and sublingual glands can also be confused with superior lymph nodes of the neck. The most likely salivary pathology in children is sialadenitis, the most common organism being *S aureus*. Treatment includes massage of the area with warm compress, antibiotic coverage for *S aureus*, sialagogues, and aggressive oral and possible intravenous hydration.

IMAGING

If the diagnosis is in question or the practitioner is considering a malignancy as a possibility, or if the infectious/inflammatory process in question may potentially require surgical intervention, such as abscess drainage, then imaging is usually required.

Ultrasonography may be conducted to further delineate the nature of the lymph node. Concerning features for malignancy on ultrasonography may include heterogeneity of the node, round shape (as opposed to oval shape), narrow or absent hilum, irregular borders, cystic necrosis, or irregular blood flow patterns to the capsule. (21) An abscess may also be diagnosed using ultrasonography; inflammatory or reactive nodes may have increased vascularity, with or without central necrosis, and soft tissue inflammation adjacent to the node. (22) On ultrasonography, abscess collections typically have a characteristic "swirling debris pattern" when the probe is pressed against the collection. This diagnostic modality may be all that is required before incision and drainage of a superficial abscess.

A CT scan may provide additional diagnostic information. Furthermore, if surgical intervention is required for deeper lymph nodes, then a CT scan with contrast is helpful in surgical planning and diagnosis. Although the risk of radiation exposure from a CT scan is low, physicians should be judicious in use of CT. An MRI provides similar information as a CT scan without the radiation exposure; however, MRI is more time-consuming and more likely to require sedation for young children. Furthermore, it may be a challenge to obtain MRI in a timely manner at many centers. For these reasons, we would advocate for judicious use of both CT and MRI. In general, these studies should be obtained when surgical management is being explored. In many uncomplicated cases of bacterial cervical lymphadenitis, physical examination with or without ultrasonography may be all that is required before initiation of a course of antibiotics. If the child does not respond after 24 to 72 hours of antibiotic treatment, then it may be appropriate to obtain a CT scan or an MRI in preparation for possible surgical intervention (Fig 5).

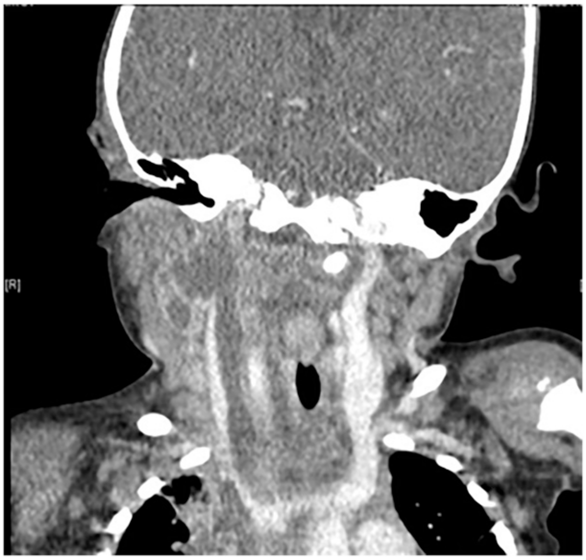


Figure 5. An 8-year-old girl with 6 days of right neck pain, fever, nausea, and vomiting was found to have a suppurative bacterial lymphadenopathy that extended into her mediastinum, requiring surgical drainage. Coronal computed tomographic scan with intravenous contrast shows the multiloculated abscess extending from the right neck and into the mediastinum.

An MRI may be preferred over a CT scan to further evaluate the lymphadenopathy if a malignancy is suspected. An MRI generally provides better resolution of soft tissue and nerve involvement, so if the practitioner suspects possible rhabdomyosarcoma or neuroblastoma then an MRI may be more useful than a CT scan. Mediastinal lymphadenopathy, diagnosed on chest radiography, has been observed in 56% of malignant cases but only 2.6% of benign cases. (23)

BIOPSY VERSUS FNA?

Patients who continue to have persistent symptoms for more than 4 to 6 weeks despite appropriate therapies may require tissue diagnosis. Patients with history, physical examination, or imaging findings consistent with malignancy should obtain a timely tissue diagnosis.

The gold standard for tissue diagnosis has been excisional biopsy. Biopsy should be considered for the following reasons: 1) suspicion of malignancy, 2) if the patient does not have resolution of lymphadenopathy over 4 to 6 weeks, 3) lymphadenopathy that steadily increases in size over 2 to 3 weeks, 4) lymphadenopathy greater than 2.0 cm, or 5) multiple lymph nodes that have concerning features on ultrasonography or CT. (24)(25) An FNA biopsy has been shown to have sensitivity of 86% and specificity of 96%. (26) Unfortunately, FNA has several limitations. Up to 20% of FNA biopsy results are nondiagnostic, requiring further interventions to ascertain a diagnosis, (27) and up to 39% of patients who undergo FNA biopsy still require further surgery for diagnosis. More importantly, FNA in young children typically requires sedation. (28) Although the complication rate of FNA is minimal, the ability to obtain a quality biopsy may be limited in the pediatric population. However, physicians should not hesitate to perform FNA biopsy in older children who are cooperative because this may often be performed without sedation and with minimal risk.

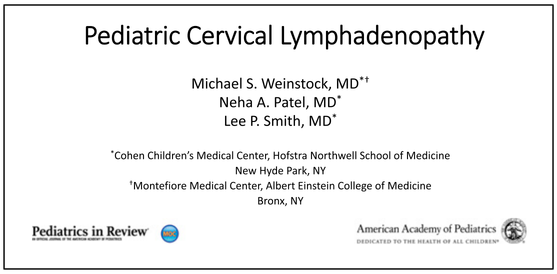
Although open excisional biopsy remains the gold standard in diagnosing persistent, worrisome lymphadenopathy, the procedure should not be undertaken lightly. Connolly and MacKenzie (29) reported complication rates of 11% in 360 patients who underwent open biopsy and excision of neck masses.

Summary

- The most common etiology for acute cervical lymphadenopathy in the pediatric population is reactivity to viral antigens. Subacute or chronic lymphadenopathy with accompanying symptoms such as malaise, sore throat, and fatigue should be evaluated for possible Epstein-Barr virus, cytomegalovirus, or even human immunodeficiency virus.
- Based on clinical evidence, ultrasonography may be a useful initial diagnostic modality. (20)(21) Sensitivity and specificity are user and institution dependent. If there is a concern for an abscess formation in an anatomically sensitive area, computed tomography or magnetic resonance imaging with intravenous contrast should be used to better delineate the anatomy.
- Based on expert and consensus opinion, a trial of 24 to 48 hours of intravenous antibiotics may be initiated for patients with small abscess formation (<1–1.5 cm in the largest dimension) because many of these patients will respond without incision and drainage.
- Abscess formation in the subacute/chronic presentation of cervical lymphadenopathy raises the concern for mycobacterial infection, *Bartonella*, or protozoan infection such as toxoplasmosis.
- Based on clinical evidence, cervical lymphadenopathy may also be caused by malignancy, although this is rare in the pediatric population. (11)(12)(13)
- Congenital neck masses, such as branchial arch abnormalities, and dermoid and thyroglossal duct cysts may masquerade as cervical lymphadenopathy. Imaging, coupled with history and physical examination, often helps to differentiate these from infectious or malignant causes.

- Salivary gland pathology may also present as a cervical neck mass or possible lymphadenopathy.
- Noninfectious causes of lymphadenopathy should also be considered in the case of subacute or chronic lymphadenopathy.
- Based on strong clinical evidence and expert opinion, biopsy of lymphadenopathy should be undertaken if there is a suspicion for malignancy, subacute/chronic lymphadenopathy, worsening lymphadenopathy despite appropriate treatment, persistent lymph nodes larger than 2 cm, or multiple lymph nodes with concerning features on computed tomography, ultrasonography, or magnetic resonance imaging. (23)(24)
- Based on clinical evidence and expert opinion, fine-needle aspiration should be considered as a diagnostic tool in patients requiring biopsy as long as they are able to tolerate the procedure under local anesthesia. (26)(27)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/9/433.supplemental.



Pediatric Cervical Lymphadenopathy

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1. A 2-year-old boy is brought to the office with swelling on the right side of the neck. He was noted to have a runny nose, fever, and a cough 7 days earlier, which are improving. The mother noted swelling on the right side of the neck 3 days earlier and states that the child is complaining of discomfort in the area of the swelling. On physical examination his temperature is 100.4°F (38°C), heart rate is 100 beats/min, and respiratory rate is 24 breaths/min. There is a 1 × 1.5-cm palpable lymph node in the right anterior cervical chain that is mildly tender but movable and with no overlying tenderness, erythema, or warmth. Nasal congestion is seen. The remainder of the physical examination findings are normal. Which of the following is the most appropriate next step in management of this patient?
   A. Chest radiograph.
   B. Fine-needle aspiration of the lymph node.
   C. Monospot test.
   D. Reassurance.
   E. Ultrasonography of the neck.
2. A 15-year-old girl is brought to the office with a sore throat, difficulty swallowing, fatigue, and persistent fever for the past 5 days. In the past 2 days she has noted increased fatigue and swollen lymph nodes in the neck. On physical examination the patient appears ill and tired. Her temperature is 101.3°F (38.5°C), respiratory rate is 18 breaths/min, and heart rate is 80 beats/min. Her oropharynx is injected with enlarged tonsils and a white exudate. Her breath is foul. Her neck shows multiple lymph nodes in the posterior cervical chain ranging in size from 0.5 to 1.5 cm in diameter. There is mild overlying tenderness. The scalp has no lesions. Examination of the heart and lungs is normal. The spleen is palpable 2 cm below the left costal margin, and the liver is not palpable. Laboratory data are as follows: white blood cell count, 15,000/µL (15 × 10^9/L); hemoglobin, 13 g/dL (130 g/L); hematocrit, 42%; platelet count, 300 × 10^3/µL (300 × 10^9/L); mean corpuscular volume, 84 μm^3 (84 fL); neutrophils, 25%; bands, 2%; monocytes, 5%; lymphocytes, 50%; atypical lymphocytes, 18%; alanine aminotransferase, 100 U/L (1.67 µkat/L) (reference range, 7–56 U/L [0.12–0.94 µkat/L]); aspartate aminotransferase, 80 U/L (1.34 µkat/L) (reference range, 10–40 U/L [0.17–0.67 µkat/L]); total bilirubin, 1.5 mg/dL (25.66 µmol/L); and rapid streptococcal antigen negative. Which of the following is the most likely diagnosis in this patient?
   A. Acute lymphocytic leukemia.
   B. Atypical mycobacterium.
   C. Cat-scratch disease.
   D. Epstein-Barr virus infection.
   E. Streptococcal pharyngitis.
3. A 3-year-old boy is brought to the emergency department with a red swollen area on the left side of the neck. The child had an upper respiratory tract infection 1 week earlier with fever and a cough. At that time the mother noted a small "swollen" area on the left side of the neck. The initial fever resolved, but over the past 2 days the fever recurred, and the swelling has gotten larger, more red, and painful. On physical examination his temperature is 101.1°F (38.4°C), respiratory rate is 18 breaths/min, and heart rate is 110 beats/min. A 2 × 2-cm red, warm, and tender lymph node is noted in the left anterior cervical chain. The node is rubbery, movable, and nonfluctuant. The oropharynx shows mild erythema with no exudates and with normal-sized tonsils. The remainder of the physical examination findings are normal. Which of the following is the most appropriate next step in the management of this patient?

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A. Computed tomography of the chest.
B. Excisional biopsy.
C. Incision and drainage of the node.
D. Oral antibiotics.
E. Ultrasonography of the neck.

4. A 12-year-old girl is brought to the office with increasing swelling above the left collar bone. She was well until 8 weeks ago when she developed a small swelling in the left lower cervical area. She was seen at an urgent care center and was treated with oral amoxicillin. The swelling did not resolve, and 4 weeks ago she was seen for follow-up in the office of her primary care provider and received a course of clindamycin. The swelling continued and is now extending above the left clavicle. The area is nontender with mild redness. She has been more tired than usual but has had no night sweats. She does not think she has lost weight. She has not had a fever since the initial presentation 8 weeks ago, when she was warm to the touch. She has no history of foreign travel and no exposure to pets or populations at risk for tuberculosis. On physical examination her weight is at the 40th percentile (was the 45th percentile at the time of her last health supervision visit 6 months ago). Her height is at the 50th percentile. Her temperature is 100.0°F (37.8°C), respiratory rate is 16 breaths/min, and heart rate is 80 beats/min. The oral cavity is normal. The neck shows a 2.5 × 3-cm firm, nontender, fixed, and nonerythematous node in the left supraclavicular area. Several smaller nodes 1.5 × 1 cm and 1 × 1 cm are noted in the left cervical chain. There are no thyroid nodules detected. The axilla and inguinal areas have no palpable lymph nodes. The remainder of the physical examination findings are normal. Results of laboratory studies (including complete blood cell count), metabolic profile, and chest radiography are normal. Which of the following is the most likely diagnosis in this patient?

A. Hodgkin lymphoma.
B. Nasopharyngeal carcinoma.
C. Neuroblastoma.
D. Rhabdomyosarcoma.
E. Thyroid carcinoma.

5. A 5-year-old boy is brought to the office by his parents due to a swelling on his neck. The mother noted this several months ago. The swelling got bigger initially but has remained the same size for the past 8 weeks. The swelling is located in the middle of his neck and moves when he sticks his tongue out. The area has occasionally been red. On physical examination a 2-cm-diameter soft mass is noted on the middle of the neck just superior to the larynx. There are no lymph nodes palpable in the cervical, supraclavicular, or axillary areas. The remainder of the physical examination findings are normal. Ultrasonography of the neck shows a normal-appearing thyroid gland with a cystic structure in the midline just superior to the larynx. A thyroid uptake scan shows a normal-appearing thyroid gland. Which of the following is the most appropriate management plan of this lesion in this patient?

A. Fine-needle aspiration.
B. I_{131} radioablation.
C. Levothyroxine.
D. Propylthiouracil.
E. Surgical excision.

Pediatric Solid Tumors in Children and Adolescents: An Overview

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Education Gaps

Pediatricians should recognize the role of age, genetic conditions, and environmental exposures in the development of malignant solid tumors in children and adolescents.

Objectives

After completing this article, readers should be able to:

1. Identify the signs and symptoms of extracranial germ cell tumors, osteosarcoma, Ewing sarcoma, thyroid cancer, and melanoma in pediatric patients.
2. Identify the genetic conditions and environmental exposures associated with different cancer types in adolescents.
3. Recognize general aspects of the multidisciplinary treatment approach in patients with extracranial germ cell tumors, osteosarcoma, Ewing sarcoma, thyroid cancer, and melanoma.

INTRODUCTION

Although hematologic and central nervous system malignancies continue to be the most common cancers in adolescents, extracranial malignant solid tumors represent, as a group, 52% of cancers in patients in the 15- to 19-year-old age group (Fig 1). The tumor distribution of malignant pediatric solid tumors in adolescents is different compared with that of younger children, in whom embryonal or developmental cancers, such as retinoblastoma, neuroblastoma, or hepatoblastoma, are more prevalent. The most common malignant solid tumors in adolescents are extracranial germ cell tumors (GCTs), bone and soft tissue sarcomas, melanoma, and thyroid cancer. The diagnosis and treatment of adolescents with cancer also have particular challenges related to patient age, such as adherence to therapy, need for psychological support, concerns about body image, and fertility preservation. In this review, we offer a general description of the clinical presentation and treatment of the most common malignant pediatric solid tumors in adolescents.

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ABBREVIATIONS

^{131}I	iodine 131
AFP	α-fetoprotein
β-HCG	β-human chorionic gonadotropin
CT	computed tomography
EWS	Ewing sarcoma
GCT	germ cell tumor
MRI	magnetic resonance imaging
OS	osteosarcoma
PTC	papillary thyroid cancer
SNL	sentinel lymph node
XP	xeroderma pigmentosum

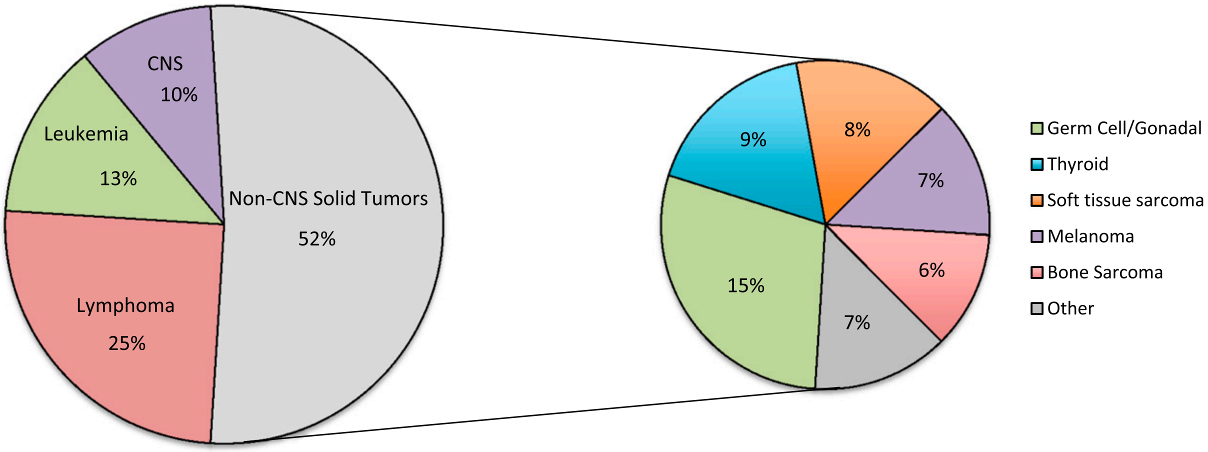

Figure 1. Distribution of pediatric cancers in adolescents aged 15 to 19 years. Extracranial solid tumors are 52% of all malignancies in this age group.

EXTRACRANIAL GCTs

Germ cell tumors are a rare and heterogeneous group of benign and malignant tumors representing a variety of histologic diagnoses and tumor locations. They arise from primordial germ cells that migrate during embryogenesis along the midline of the body to the gonadal ridges and differentiate into ovarian and testicular tissues. Germ cell tumors can arise in any of the sites along the migration path. Although GCTs also occur in the brain, in this review we focus on those occurring outside of the central nervous system. These tumors occur most frequently in adolescents, representing 14% of cancers between ages 15 and 19 years. Also, GCTs may present in the fetal/neonatal age group, most commonly as benign teratomas of the head and neck, retroperitoneum, or sacrococcygeal region.

Children with disorders of sex development are at increased risk for GCTs. Children with Swyer syndrome (XY gonadal dysgenesis), in which patients are phenotypically female but have a male karyotype and gonadal dysgenesis, are at increased risk for malignant transformation of the nonfunctional gonadal tissue. Klinefelter syndrome (47,XXY) and Turner syndrome (45,XO) are associated with mediastinal GCTs and gonadoblastoma, respectively. Although gonadectomy is recommended for some individuals with disorders of sex development, this determination should be made based on a multitude of factors, including karyotype, molecular and hormonal data, gonadal morphology, and psychosocial factors, including individual comfort with risk of GCT. In addition, boys with cryptorchidism are at higher risk for testicular GCTs. Orchidopexy before puberty reduces this risk.

Germ cell tumors can be categorized based on location and histologic features. Gonadal GCTs occur in the ovaries or testis, and extragonadal GCTs are found in midline sites, including the head and neck, mediastinum, retroperitoneum, or sacrococcygeal region. Histologically, they are categorized into teratomas (mature or immature) or malignant GCTs. Teratomas are the most common histologic subtype of GCT, with mature being more common than immature teratomas. Mature teratomas are benign tumors, comprised entirely of well-differentiated tumors from all 3 germ cell layers (ectoderm, mesoderm, and endoderm). Although any tissue type may be found in a mature teratoma, the most common are skin, adipose, intestinal, and cystic structures lined by epithelium. In addition to containing tissues from the 3 germ cell layers, immature teratomas also contain variable amounts of immature tissue, primarily neuroepithelial in origin. Immature teratomas are graded according to the amount of immature neural tissue found, from 0 to 3, and higher grades are more likely to exhibit malignant behavior. Malignant GCTs are a heterogeneous group of tumors classified according to their cell of origin and location. Tumors containing 2 or more histologic subtypes are termed *mixed malignant GCTs* (Table 1).

Clinical Presentation and Diagnosis

The clinical presentation of GCTs in children is variable, reflecting the heterogeneity of histology and tumor locations. Metastatic disease occurs in 20% of patients and is most commonly found in the lungs, but it may also involve bone, liver, and brain. Testicular GCTs present as a painless swelling of 1 testis and ovarian CGTs usually present with gradual onset of abdominal distention. Acute onset of pain may suggest ovarian torsion from tumor or intratumoral hemorrhage, requiring prompt evaluation. Identification of any midline tumor should prompt consideration of a GCT. Mediastinal tumors present with symptoms related to compression of structures in the mediastinum, including airway

TABLE 1. **Extracranial Germ Cell Tumors (GCTs)**

TUMOR HISTOLOGY	COMMON TUMOR LOCATIONS
Teratomas	
Mature teratoma	Mediastinum, sacrococcyx, ovary, testis
Immature teratoma	Sacrococcyx, ovary
Malignant GCTs	
Yolk sac tumor	Sacrococcyx, testis, ovary
Germinoma	Mediastinum, testis (seminoma), ovary (dysgerminoma)
Embryonal carcinoma	Testis
Choriocarcinoma	Mediastinum, ovary
Gonadoblastoma	Dysgenetic gonads (phenotypic female subjects)
Mixed GCTs	Extragonadal, ovary, testis (tumors contain ≥2 of the malignant histologies listed above)

compression, superior vena cava syndrome, or heart failure. Sacrococcygeal teratomas are the most common GCTs in infants and generally are diagnosed either by prenatal ultrasonography or at the time of birth. These unique tumors are classified according to the degree of externalization versus internalization. Type I to III tumors present with visible or palpable masses in the sacrococcygeal region. Type IV tumors may present with constipation, pain, or symptoms of spinal cord dysfunction. Evaluation of the primary tumor site includes ultrasonography for testicular tumors and cross-sectional imaging with magnetic resonance imaging (MRI) or computed tomography (CT) for all other sites. Chest CT should be performed to evaluate for lung metastasis. Whole-body bone scan and/or MRI of the brain is obtained if the patient has symptoms consistent with involvement of these sites as well as in those with metastatic choriocarcinoma. The definitive diagnosis is made from histologic examination of tumor tissue obtained from biopsy or resection of the mass depending on the location and extent of disease at presentation. Serum tumor markers can be very useful in the diagnosis and monitoring of progression and recurrence of GCTs. α-Fetoprotein (AFP) is produced in early embryogenesis by the yolk sac. Elevated serum AFP levels in patients with GCTs indicate the presence of malignant components such as yolk sac or embryonal carcinoma. In young infants, serum AFP levels can be difficult to interpret because AFP levels at birth are variable and the half-life varies during the first year of life. Elevations in AFP levels are also associated with hepatoblastoma and some benign liver conditions. β-Human chorionic gonadotropin (β-HCG) is another serum marker used in the diagnosis and monitoring of GCTs. β-Human chorionic gonadotropin is normally produced by the placenta and its elevation in patients with GCTs indicates the presence of elements related to syncytiotrophoblasts, often found in germinomas, choriocarcinoma, or embryonal carcinoma. Similar to AFP, β-HCG levels may also be elevated in non-GCT malignancies, including neuroendocrine tumors and hepatic tumors, and in nonmalignant conditions resulting in elevation in luteinizing hormone. In addition to AFP and β-HCG, other tumor markers used in the detection and monitoring of GCTs include inhibin, estrogen, and testosterone.

Tumor Staging and Treatment

Staging of GCTs is complex, varies among different cooperative oncology groups, and is beyond the scope of this review. Tumor site and stage are combined to assign patients to risk treatment groups, which are also variable across cooperative oncology groups, but generally include a low-risk classification managed with surgical resection and surveillance, an intermediate-risk group of patients who have excellent outcomes with chemotherapy-based regimens, and a high-risk group for whom outcomes are poor with current treatment modalities. Treatment for mature teratomas is surgical resection alone. Particularly for sacrococcygeal teratomas, complete resection is important to reduce the risk of recurrence. Although surgical resection is also the mainstay of treatment for immature teratomas, the use of adjuvant chemotherapy is controversial. Gynecologic oncologists traditionally have treated women with ovarian immature teratomas with chemotherapy based on a study reporting high recurrence rates in these patients with surgery alone. However, pediatric trials have not demonstrated similar results, and pediatric oncologists have not generally given chemotherapy to this population.

Malignant GCTs are treated with surgical resection followed by chemotherapy. However, no study has clearly demonstrated superior outcomes for those with up-front surgical resection before chemotherapy; therefore, when the risk of surgical resection is high, chemotherapy may be given in an attempt to shrink the tumor before proceeding with surgery. Surgical approaches vary based on the anatomical location of the tumor. Importantly, surgical resection of testicular tumors should use an inguinal approach rather than a trans-scrotal approach due to potential contamination of lymphatic channels in the scrotum and upstaging of the patient. Ovarian masses suspicious for malignancy should be resected with the ovary and mass intact with the intent to keep the capsule intact. Complete surgical staging, including peritoneal washings and inspection of the contralateral ovary, retroperitoneal lymph nodes, and omentum, is required to determine disease stage and guide chemotherapy decision making. Adjuvant chemotherapy with platinum-based regimens have dramatically increased the survival of patients with malignant CGTs. Patients with stage 1 testicular and ovarian malignant GCTs are generally not treated with chemotherapy; however, those with stage 2 and higher, as well as all patients with extragonadal GCTs, are treated with a variable number of cycles of chemotherapy regimens containing cisplatin, etoposide and bleomycin.

The outcomes for children with GCTs are excellent overall. Prognosis depends on stage of disease, histologic features, age of the patient, and location of the tumor. For many groups, overall survival approaches 100%, although the prognosis of high-risk patients with metastatic disease remains dismal. Unlike many other solid tumors in children, salvage therapy after tumor relapse is often successful for GCTs. The focus of recent clinical trials has been on reducing exposure to chemotherapy drugs to reduce the incidence of late effects, including hearing loss, renal injury, and pulmonary toxicity. In addition, collaborations between pediatric and adult cooperative groups are under way to standardize the staging, risk stratification, and treatment approaches for patients with GCTs.

OSTEOSARCOMA

Osteosarcoma (OS) is the most common malignant bone tumor in children and adolescents and accounts for 2.8% of all pediatric cancers. Each year in the United States there are an estimated 450 new cases of OS diagnosed in patients younger than 20 years. The incidence of OS is slightly higher in males and in African American children. The median age at diagnosis is 16 years, with most patients being diagnosed between ages 14 and 19 years. Most cases of OS occur in children with no family history of cancer or associated conditions, but a minority of cases are diagnosed in patients with cancer predisposition syndromes, such as Li-Fraumeni syndrome (mutations in the *TP53* gene), hereditary retinoblastoma (mutations in the *RB* gene), and Rothmund-Thomson syndrome (mutations in the *REQL4* gene). A small number of OS cases also arise in patients who have previously received radiotherapy.

Clinical Presentation and Diagnosis

The most common presenting symptom is pain with or without a visible enlarging mass. Most cases of OS arise around the knee, in either the metaphysis of the distal femur or proximal tibia, and the next most common site is in the hip or pelvis. Tumors are usually first identified on plain radiographs, typically demonstrating aggressive periosteal reactions with the classic sunburst pattern and Codman triangle (Fig 2A). Radiographs may also show a pathologic fracture associated with the tumor. A contrast-enhanced MRI of the affected area should be obtained before tumor biopsy for planning purposes. If the lesion is in an extremity, the MRI should extend to the joints above and below the affected bone to evaluate for extent of involvement. A tumor biopsy is required to establish the diagnosis and should be performed at an institution familiar with processing malignant bone tumors. Historically, open biopsy has been the preferred tumor biopsy method for diagnostic purposes. Recent advances in interventional radiology techniques using core needle biopsies combined with fine-needle aspiration (FNA) have proved to also be highly accurate to establish the diagnosis of OS. Once the diagnosis of OS is established, a metastatic evaluation including a noncontrast CT scan of the chest to evaluate for lung metastasis and a technetium-99 whole-body bone scan to evaluate for other bony lesions should be completed.

Tumor Staging and Treatment

Osteosarcoma is classified as localized (nonmetastatic) or metastatic. The presence of metastasis at diagnosis remains the strongest predictor of clinical outcome. Approximately 20% of patients will be diagnosed as having distant metastatic disease at the time of diagnosis. The most common site of metastasis is the lungs, followed by other bones. The standard treatment approach for patients with OS includes neoadjuvant chemotherapy, followed by surgical resection and then consolidative chemotherapy. Complete surgical resection of the primary tumor is critical in OS and should be performed by an experienced oncologic orthopedic surgeon. Although amputation of an affected limb is always an option for tumors in the extremities, most patients are now able to have a limb-sparing procedure. Limb salvage options include endoprosthesis placement, bone grafting, or rotationplasty. Patients with lung metastases should undergo thoracotomies during consolidation chemotherapy to remove any detectable lesions by manual surgical exploration. Bilateral thoracotomies should be considered even if all lesions have resolved on chest CT because small lesions can persist that are not visible on imaging yet can be palpated by the surgeon for removal.

The outcomes for children and adolescents with OS vary widely depending on metastatic status. Patients with localized disease have 5-year overall survival of approximately 70% to 75%, but patients with metastatic disease have 5-year

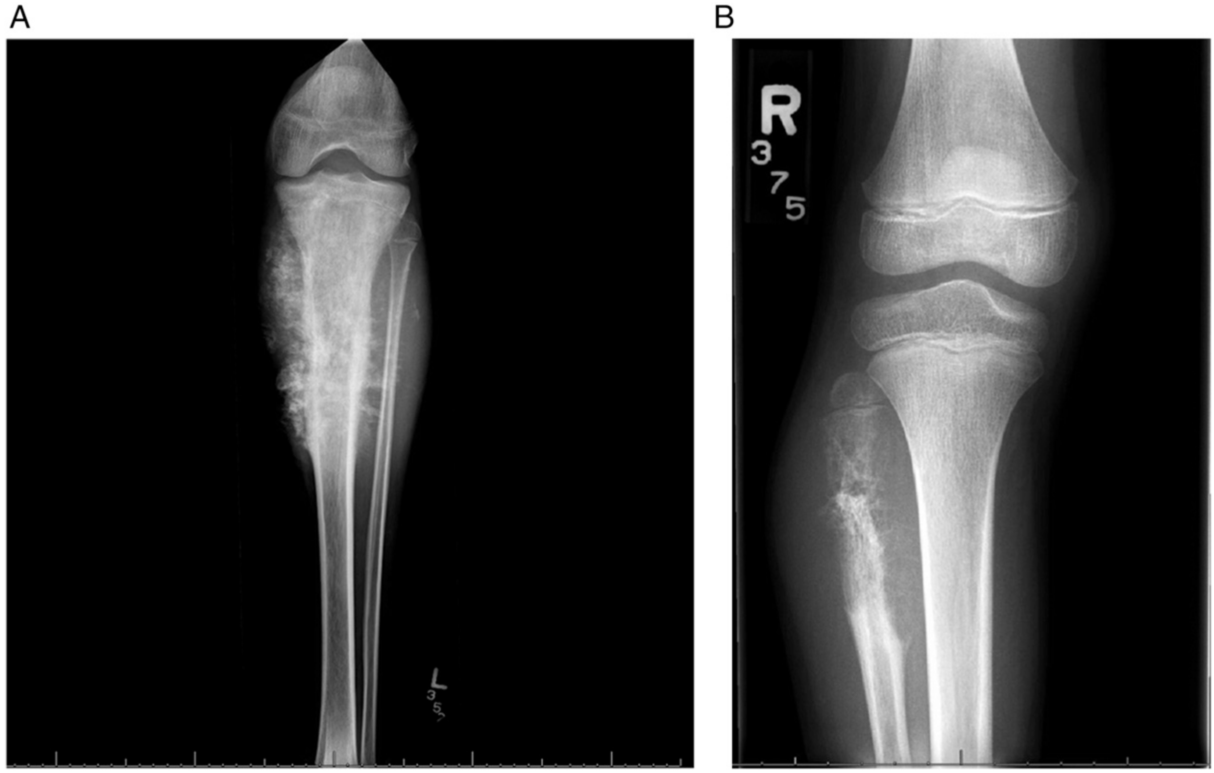

Figure 2. A. Aggressive periosteal reaction with the sunburst pattern in the proximal tibia of a patient with osteosarcoma. B. Destructive lesion with moth-eaten appearance of the proximal fibula in a patient with Ewing sarcoma.

overall survival of less than 30%. Patients with metastatic disease to the lungs have a slightly better survival rate than patients with multiple bones involved. Patients with both lung and bone metastasis have extremely poor outcomes. In addition, the percentage of tumor necrosis after neoadjuvant chemotherapy is prognostic, and patients with greater than 90% tumor necrosis have better outcomes than those with less tumor necrosis. The focus of recent clinical trials has been to intensify treatment for patients with metastatic disease and poor tumor necrosis, but the results have been disappointing and currently the treatment remains the same for both localized and metastatic disease, except for surgical resection of all sites of metastasis.

EWING SARCOMA

Ewing sarcoma (EWS), the second most common malignant bone tumor in children and adolescents, accounts for approximately 1.9% of all pediatric cancers. Each year in the United States there are an estimated 300 new cases of EWS diagnosed in patients younger than 20 years of age. The median age at diagnosis is 15 years, and most patients are diagnosed between ages 12 and 18 years. The incidence of EWS is slightly higher in males and in white children. Approximately 20% of EWS arise in extraosseous locations. Unlike OS, there are no cancer predisposition syndromes associated with EWS.

Clinical Presentation and Diagnosis

Patients with EWS often present with pain to the affected area with or without a palpable mass. Patients may also present with a limp or refusal to bear weight on the affected limb. Unlike OS, EWS can also present with systemic symptoms such as fever, fatigue, and weight loss. The most common site for EWS is the lower extremities (femur, tibia, and fibula), and lesions are often centered in the diaphysis of the long bones. Approximately 20% of EWS lesions are considered extraosseous, arising in the soft tissues. The trunk is the most common site for these extraosseous EWS tumors.

In primary bone EWS, plain radiographs may have a moth-eaten appearance of the affected bone or an onion skin periosteal reaction (Fig 2B). There is often a substantial soft tissue component of primary bone EWS tumors that may be visible on radiographs. Similar to OS, a contrast-enhanced MRI of the affected area should be obtained before tumor biopsy for planning purposes, and for extremity tumors, the MRI should extend to the joint above and below the affected bone to evaluate for extent of involvement. The definitive diagnosis of EWS is made through tissue biopsy, either an open biopsy performed by an oncology surgeon or core needle biopsy performed by an interventional radiologist. Nearly all EWS tumors have a pathognomonic chromosomal translocation involving the *EWSR1* gene, which is found on the long arm of chromosome 22. The 2 most common translocation partners are FLI1 and ERG, which account for approximately 95% of translocation partners in EWS, and the resultant fusion proteins are oncogenes. Tumor biopsy samples of suspected EWS cases should be sent for molecular testing of the EWSR1 translocations with either fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction using specific primer sets. Once the diagnosis of EWS is confirmed, a metastatic evaluation should be completed, including a noncontrast CT of the chest, bilateral bone marrow aspirate and biopsies, and either a technetium-99 whole-body bone scan or a positron emission tomographic (PET) scan.

Tumor Staging and Treatment

Similar to OS, EWS is classified as metastatic or localized, and the presence of metastasis at diagnosis remains the strongest predictor of outcome. Approximately 25% of patients will be diagnosed as having distant metastatic disease at the time of diagnosis. The most common site of metastasis is the lungs, followed by other bones, bone marrow, and, rarely, lymph nodes. The standard treatment of EWS includes neoadjuvant chemotherapy, followed by local control of the primary tumor and consolidative chemotherapy. If the primary tumor is surgically resectable, surgery is the treatment of choice, with the goal of complete resection. Unlike OS, EWS is radiation sensitive; thus, radiotherapy is an alternate mode of local control for patients with unresectable tumors. All patients with lung metastases should undergo bilateral lung irradiation at the end of therapy even if lesions have resolved on chest CT. There is no role for surgical resection of lung metastases in EWS.

The outcomes for children and adolescents with EWS depend on metastatic status and site of disease. Patients with localized disease have 5-year overall survival of approximately 70% to 75%, but patients with metastatic disease have 5-year overall survival of 15% to 30%. Patients with distal extremity tumors have better outcomes than those with proximal or pelvic tumors, which may be due to the increased likelihood of complete surgical resection for distal extremity lesions. In addition, patients younger than 10 years, including infants, tend to have better outcomes than older patients for unclear reasons. The most recent cooperative trial in the United States showed improved outcomes for localized patients with increased dose intensity by compressing chemotherapy cycles to every 2 weeks as opposed to every 3 weeks. Current clinical trials are under way to identify novel agents for patients with metastatic disease.

THYROID CANCER

Thyroid carcinoma is the second most common extracranial solid tumor in adolescents (15–19 years old). There are approximately 1,100 new cases in the United States every year. Females are 5 times more affected than males and adolescents have an almost 10-fold greater incidence of thyroid cancer than young children. There has been an increased incidence of thyroid cancers in adolescents in the past 20 years in the United States for reasons that are unknown. This increased trend cannot be solely attributed to early detection because the number of thyroid cancers was greater for all tumor sizes. Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, representing more than 90% of cases. Follicular, medullary, and anaplastic thyroid cancers are rare in children. The following review focuses on PTC.

The risk of developing PTC is significantly increased in children exposed to ionizing radiation. A decade after the Chernobyl nuclear accident, childhood survivors had a 10-fold increased incidence of PTC. Young children, particularly those younger than 5 years, previously treated with radiotherapy for head, neck, or mediastinal cancers have an increased risk of PTC up to 25 years after radiation exposure. There are several genetic disorders that predispose to thyroid cancer. Patients with *APC*-associated polyposis, *PTEN* hamartoma syndrome, *DICER1* syndrome, Carney complex (mutation on *PRKAR1A* gene), Werner syndrome (mutation on *WRN* gene), or familial nonmedullary thyroid cancer have an increased incidence of thyroid cancer. Patients at increased risk for PTC should have an annual physical examination to assess for palpable thyroid nodules, thyroid gland asymmetry, or cervical lymphadenopathy, and should be referred to specialized centers for appropriate follow-up and genetic counseling.

Clinical Presentation and Diagnosis

Patients with PTC usually present with a painless thyroid mass and/or enlarged cervical lymph nodes. Thyroid nodules diagnosed in children have a greater risk of malignancy (26%) compared with those in adults (5%–10%). Children with PTC are also more likely to present with regional lymph node involvement (up to 50%), extrathyroidal extension, and lung metastasis (20%–30%) than adults. Another difference between pediatric and adult PTC is the frequency of different gene tumor mutations; *RET/PTC* gene rearrangement and *BRAF* mutation are the most common mutations observed in pediatric PTC.

The initial evaluation of children with solitary thyroid nodule should include high-quality thyroid ultrasonography and serum thyrotropin, serum thyroglobulin, and thyroglobulin antibody levels. Patients should undergo nuclear thyroid scintigraphy if thyrotropin levels are suppressed to differentiate between a hypofunctioning or hyperfunctioning thyroid nodule. An FNA under ultrasonography guidance of the thyroid nodule should be strongly considered if the patient has risk factors for thyroid cancer, the presence of "malignant" features on ultrasonography (hypoechogenicity, irregular margins, increased intranodular blood flow, or microcalcifications), a hypofunctioning nodule, or nodule size greater than 1 cm. Surgery (lobectomy plus isthmusectomy) may be considered in patients with hyperfunctioning nodules.

Tumor Staging and Treatment

Once the diagnosis of PTC is established, patients should have a comprehensive evaluation of the neck by ultrasonography using a high-resolution probe and Doppler technique. A contrast-enhanced CT scan of the chest and neck should be considered for those with evidence of cervical lymph node involvement. There is no role for routine use of whole-body bone scan or PET/CT scan in PTC.

Overall, the clinical outcome of children and adolescents with PTC is excellent, with 10-year survival of nearly 100% even in patients who present with distant metastases. The treatment of PTC includes surgical resection of the thyroid gland, dissection of cervical lymph nodes, and administration of radioactive iodine. For patients with PTC, total thyroidectomy is the recommended treatment of choice, which should ideally be performed by an experienced surgeon. Lateral neck dissection is performed only in patients with histologic confirmation of lymph node involvement and should not be done routinely for prophylactic purposes. The surgical complications of total thyroidectomy include hypoparathyroidism secondary to removal of parathyroid glands and recurrent laryngeal nerve damage.

A whole-body scan is obtained within 12 weeks after total thyroidectomy to identify residual disease and the presence of lung metastasis. The use of radioactive iodine ablation with iodine 131 (^{131}I) is recommended in patients with persistent or unresectable locoregional/nodal disease and distant metastasis. This treatment may be provided more than once and requires special preparation, withdrawing levothyroxine supplementation for at least 14 days to facilitate ^{131}I uptake by tumor cells. The late effects of ^{131}I therapy include salivary gland dysfunction, bone marrow suppression, and increased risk of secondary malignancies.

The American Thyroid Association Task Force on Pediatric Thyroid Cancer published a guideline for the management of thyroid nodules and treatment of PTC in 2015. These guidelines recommended categorizing patients with PTC into 3 risks groups (low, intermediate, and high risk) based on tumor extension at diagnosis to determine the extent of postoperative evaluation, to identify patients who would benefit from ^{131}I therapy, and to establish the frequency of surveillance evaluations. The American Thyroid Association guidelines also emphasized that children with PTC should be evaluated in specialized centers by a multidisciplinary team.

MELANOMA

Melanoma is the most common skin cancer in children and adolescents. There are approximately 300 to 500 new cases in the United States every year. Melanoma annual incidence increases with age and accounts for approximately 7% of all cancers in adolescents. Although the incidence of pediatric melanoma increased by 2% per year between 1973 and 2009 in the United States, a recent review suggests a decrease of the incidence of melanoma in children from 2000 to 2010. This decrease in incidence may be related to changes in sun protection practices and imposed limitations to the use of artificial tanning devices in young people.

Some genetic conditions increase the risk of developing melanoma. Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by extreme sensitivity to UV light, keratosis, and neurologic manifestations. Patients with XP carry a genetic defect that significantly impairs the ability to repair DNA damage after UV light exposure. Approximately 5% to 13% of patients with XP will develop melanoma by age 21 years, and most affected individuals will develop nonmelanoma skin cancers by age 8 years. Protection from sunlight and early detection of malignant skin lesions are essential in these children.

Familial atypical multiple mole and melanoma syndrome is an autosomal dominant condition associated with mutations in the *CDKN2A* gene. These patients have a family history of melanoma and carry an increased risk of melanoma and pancreatic cancer. These individuals often develop more than 50 atypical nevi throughout their lives and require close clinical follow-up, protection from sun exposure, and genetic counseling. Patients with congenital melanocytic nevi also have an increased risk of developing melanoma during their lifetime. These melanocytic lesions are multiple, may be small or very large (>20 cm), and may have multiple satellite nevi. Approximately 2.5% of patients with large lesions develop melanoma. For half of these children, melanoma develops in the first 5 years of life. The recommended treatment is prophylactic excision of big lesions if feasible.

Immunosuppression, both congenital and acquired, is a well-established risk factor for melanoma. Individuals with immunodeficiency conditions, such as chronic granulomatous disease or human immunodeficiency virus, and organ transplant recipients have a 3- to 6-fold increased risk of developing melanoma; therefore, children with immunosuppression should have a complete skin examination as part of their regular clinical evaluation.

The most common risk factor associated with both melanoma and nonmelanoma skin cancers is sun exposure. The American Academy of Pediatrics recommends wearing proper clothing and hats, applying sunscreen, wearing sunglasses, and avoiding sun exposure between 10 AM and 4 PM, when the sun's rays are strongest. The use of artificial tanning devices is discouraged, and access to tanning salons is prohibited in children younger than 18 years in many parts of the United States.

Clinical Presentation and Diagnosis

The diagnosis of melanoma in children can be challenging because skin lesions usually do not have the ABCDE features (**A**symetry, irregular **B**orders, uneven **C**olor distribution, **D**iameter >6 mm, **E**volving nevus) observed in adult patients with melanoma. Salient characteristics in pediatric melanoma are the presence of amelanocytic lesions and their evolution over time. Modified ABCDE criteria have been proposed for children with suspicious lesions (Table 2). Clinical evaluation of pediatric melanoma involves a comprehensive skin examination including mucosal surfaces, interdigital spaces, and palpation of lymph nodes adjacent to any suspicious skin lesions. The diagnosis of melanoma is established after performing an excisional biopsy. The entire lesion should be removed, including the subcutaneous fat, with 3-mm margins if possible. An experienced dermatopathologist should evaluate the biopsy due to the existence of distinct melanocytic lesions with atypical features that share some histologic characteristics with benign nevi and melanoma. These lesions, named Spitz tumors or nevi, may be benign but can be indistinguishable pathologically from melanoma. Therefore, Spitz tumors should be completely excised with clear margins and initially managed as melanoma. Comprehensive genomic studies such as fluorescence in situ hybridization or genomic sequencing may help to definitively differentiate these melanocytic lesions in the near future. We recommend that patients with a diagnosis of Spitz tumors/nevi be referred to specialized cancer centers for diagnostic confirmation and additional evaluation.

TABLE 2. Modified ABCDE Criteria for Pediatric Melanoma

A = **A**symmetry/**A**melanocytic (flesh colored, pink, red, pyogenic granuloma-like appearance)

B = irregular **B**orders/**B**leeding (ulceration), bumps (papulonodules, raised lesions)

C = uneven **C**olor distribution or uniformity

D = **De** novo development, any **D**iameter (may be <6 mm)

E = **E**volution (increase in diameter or elevation)

Adapted from Cordoro KM, Gupta D, Frieden IJ, McCalmont T, Kashani-Sabet M. Pediatric melanoma: results of a large cohort study and proposal for modified ABCD detection criteria for children. J Am Acad Dermatol. *2013;68(6):913–925.*

Tumor Staging and Treatment

The diagnostic and tumor staging evaluation of melanoma includes full excision of the lesion, assessment of regional lymph nodes, and evaluation of distant metastatic disease. Melanoma thickness determines the extent of the surgical resection and subsequent lymph node evaluation. The use of sentinel lymph node (SLN) biopsy, a surgical procedure that allows the identification of micrometastasis in the regional lymph node basin, is controversial in pediatric patients with melanoma and should be addressed on a case-by-case basis. Some authors recommended that SLN biopsy be performed in patients with lesions measuring more than 1 mm in thickness or thin lesions (<1 mm) with unfavorable features, such as ulceration or a high mitotic rate. Patients with clinical evidence of locoregional tumor involvement (enlarged lymph nodes) would need a complete blood cell count, serum lactate dehydrogenase levels, and CT scans of the chest, abdomen, and pelvis. Patients with evidence of distant metastases on CT images may also require an MRI of the brain and whole-body PET/CT to complete tumor staging and guide further treatment.

In the absence of pediatric-specific disease staging and treatment recommendations, treating physicians generally follow adult guidelines. The most important predictor of prognosis for pediatric melanoma is stage at diagnosis. Overall survival for pediatric patients with melanoma, considering all disease stages, is 90%. Surgical excision is the treatment of choice for localized melanoma. The recommended margins vary based on thickness of the lesion, from 0.5 cm for melanoma in situ to 2 cm for tumor thickness greater than 2 mm. However, cosmetic and functional aspects should be taken into consideration in children because these margins may not be feasible or necessary. The recommendation that regional lymphadenectomy should be considered in patients with positive SLN is based on data from adult melanoma clinical trials. However, this procedure carries significant risks, including surgical site infection, lymphedema, and nerve injury. Moreover, there is no clear evidence that performing regional lymphadenectomy in children with positive SLNs decreases local tumor recurrence or increases survival. Pediatric patients with positive SLNs who do not undergo regional lymphadenectomy should be monitored closely with frequent clinical evaluations and ultrasonography surveillance of the positive nodal basin. Regional lymphadenectomy is recommended in pediatric patients who present with clinical evidence of regional lymph node involvement that is confirmed by histologic analysis.

Pediatric patients with high-risk melanoma can receive adjuvant therapy with high-dose interferon alfa-2b, although recently, immunotherapy and targeted therapy are more favored treatment approaches. The use of immunotherapy to treat metastatic melanoma constitutes a milestone in the history of cancer research and treatment. Ipilimumab, a monoclonal antibody that binds CTLA-4 and boosts the immune system response against cancer cells, is approved to treat adults and children older than 12 years with unresectable or metastatic melanoma. Currently, there are several clinical trials aiming to study the effect of different anticancer agents, such as pembrolizumab (PD-1 inhibitor), dabrafenib (BRAF inhibitor), and ipilimumab (CTL-4 antibody) in younger children with melanoma. The results of these ongoing clinical trials may significantly affect the clinical outcome of pediatric patients with metastatic or recurrent melanoma.

ACKNOWLEDGMENT

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Summary

- Based on strong research evidence, the incidence and type of malignant solid tumors are different in adolescents and young children.
- Based on strong research evidence, melanoma and thyroid cancers are common malignancies in adolescents; therefore, comprehensive skin and thyroid gland examinations should be performed as part of regular well-child care visits in this population.
- Based on strong research evidence, malignant solid tumors in adolescents are managed by surgery, chemotherapy, and radiotherapy depending of the tumor type and stage. Children with cancer should be promptly referred to specialized centers for appropriate diagnosis and treatment.
- Based on strong research evidence, the enrollment of adolescents with cancer in clinical trials should be considered to optimize different treatment approaches and reduce the development of long-term health problems.

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1. A 3-year-old boy, new to your practice, is brought by his parents for an initial visit. On physical examination he is noted to have a left undescended testicle. The right testicle is palpated in the scrotal sac and is of normal size. You discuss with the parents the plan of care. Which of the following is the best next step in the management of this patient?
   - A. Annual screening of α-fetoprotein levels.
   - B. Annual testicular ultrasonography.
   - C. Gonadectomy.
   - D. Hormone therapy if the testicle does not descend by the time he reaches full adult height.
   - E. Orchiopexy before puberty.
2. A 14-year-old boy with a history of retinoblastoma as an infant presents with pain in his left thigh. A radiograph of the left leg reveals a periosteal reaction with a sunburst pattern in the metaphysis of the distal femur. Which of the following is the most likely diagnosis in this patient?
   - A. Ewing sarcoma.
   - B. Chondrosarcoma.
   - C. Metastatic retinoblastoma.
   - D. Osteomyelitis.
   - E. Osteosarcoma.
3. A 16-year-old girl presents with a 1-month history of fever, fatigue, weight loss, and pain on the chest wall. On physical examination there is a palpable 5-cm soft tissue mass overlying the fifth rib. Which of the following is the most likely diagnosis in this patient?
   - A. Ewing sarcoma.
   - B. Germ cell tumor.
   - C. Melanoma.
   - D. Osteomyelitis.
   - E. Osteosarcoma.
4. A 15-year-old girl, who received treatment for medulloblastoma at 4 years of age, presents for a routine health maintenance visit. On physical examination there is a nontender mass over her thyroid gland and associated cervical lymphadenopathy. Diagnostic evaluation confirms the diagnosis of papillary thyroid cancer. Which of the following is the most appropriate initial management in this patient?
   - A. Lateral neck dissection.
   - B. Neoadjuvant chemotherapy.
   - C. Radiation to the neck.
   - D. Radioactive iodine ablation.
   - E. Total thyroidectomy.
5. A 16-year-old boy with a history of cardiac transplant at 8 years of age presents for a routine health maintenance visit. On physical examination a skin lesion is noted on the back of his neck. Which of the following features of this skin lesion would be most concerning for melanoma in this patient?
   - A. Flat (nonraised) appearance.
   - B. Hyperpigmentation.
   - C. Regular borders.
   - D. Symmetry.
   - E. Ulceration.

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Pediatric Hip Disorders: Slipped Capital Femoral Epiphysis and Legg-Calvé-Perthes Disease

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Practice Gaps

1. The differential diagnosis for a limping child or adolescent with hip or knee pain is broad. Delayed or missed diagnoses of slipped capital femoral epiphysis and Legg-Calvé-Perthes disease have significant morbidity. Clinicians should understand when to suspect these disorders based on history, examination, and early imaging findings to allow for timely referral to a specialist.
2. Clinicians should also have a basic understanding of the treatment options and prognosis of these disorders to counsel patients and their families before and during treatment by a specialist.

Objectives After completing this article, readers should be able to:

1. Identify the general anatomy relevant to slipped capital femoral epiphysis (SCFE) and Legg-Calvé-Perthes disease (LCPD) pathology.
2. Recognize the symptoms and physical examination findings of SCFE and LCPD.
3. Know the basic laboratory values and imaging to order to evaluate for SCFE and LCPD when referring to a specialist.
4. Differentiate straightforward presentations of SCFE and LCPD.
5. Understand broad treatment categories and the prognoses of SCFE and LCPD.
6. Realize the importance of timely referral to a specialist for SCFE and LCPD.

INTRODUCTION

Pediatric hip pathology can lead to devastating complications, such as hip instability, early arthritis, and growth abnormalities. Two of the most common pathologies in this age group include slipped capital femoral epiphysis (SCFE) and Legg-Calvé-Perthes disease (LCPD). The importance of early diagnosis is paramount in both of these disorders, to allow for early treatment and attempt to limit the potentially morbid outcomes. Because many of these children will

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ABBREVIATIONS

AP	anteroposterior
LCPD	Legg-Calvé-Perthes disease
MRI	magnetic resonance imaging
SCFE	slipped capital femoral epiphysis

initially present to their pediatrician, recognition and early referral to an orthopedic specialist can drastically change their outcomes.

SLIPPED CAPITAL FEMORAL EPIPHYSIS

Background, Pathophysiology, and Relevant Anatomy

Slipped capital femoral epiphysis is the most common hip pathology affecting adolescents. (1) Although a common diagnosis, up to 20% of patients are delayed in diagnosis, with short- and long-term consequences. (2) Contradictory to its name, the pathologic process occurs when the femoral head (epiphysis) of the proximal femur displaces on the femoral neck due to weakness in the hypertrophic zone of the growth plate (physis). Figure 1 illustrates the anatomy of the physis and epiphysis. Factors that may contribute to this slippage either predispose an individual to increased stress across the physis, such as obesity, or decrease its resistance to shear forces, such as metabolic derangements (ie, hypothyroidism) that inherently weaken the physis. (1) The pathogenesis of SCFE is likely multifactorial, with anatomical, genetic, and temporal factors.

Increased shear forces across the physis may predispose individuals to slippage. (1)(3) Obese children tend to have higher mechanical loads across the physis and of the proximal femur, with increased retroversion. (1)(4) As childhood obesity continues to rise, so too does the prevalence of SCFE. (4) Obesity and puberty may be risk factors for SCFE due to changes in the metabolic activity of the physis. (5) The natural history of SCFE is affected by the acuity at presentation (ie, acute versus chronic SCFE), degree of displacement of the femoral neck in relation to the epiphysis, stability of the physis, and the resulting relation of the proximal femoral metaphysis to the femoral head. (1)

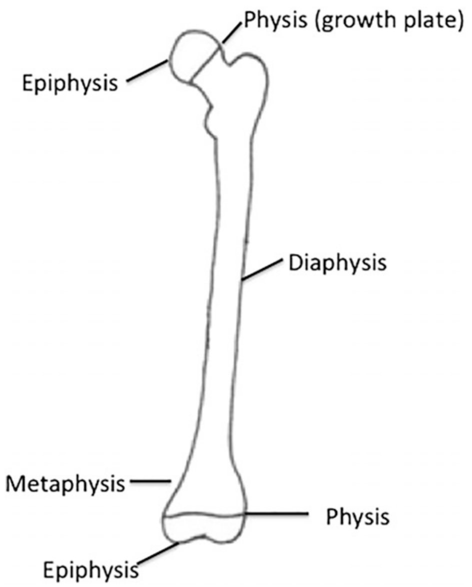


Figure 1. The femoral head is known as the epiphysis. Growth of the proximal femur occurs at the growth plate, known as the physis. The femoral shaft is known as the diaphysis. The metaphysis is where the diaphysis transitions into the epiphysis.

Epidemiology

Slipped capital femoral epiphysis is the most common hip pathology affecting adolescents, and the incidence continues to rise. (1)(3)(4)(6) The average age at onset is 12.7 years (13.5 years in boys and 12.0 years in girls). Unfortunately, recent evidence has shown that the average age at presentation has been dropping, which has been correlated with the rise in pediatric obesity. (4)(7)(8)(9) The overall prevalence of the disorder varies from 0.71 to 10.8 per 100,000 children, with boys more often affected than girls at a ratio of approximately 1.5:1. (1)(10) Typically, SCFE presents during puberty due to the relative weakness of the physis during rapid growth. (5)

Loder et al (11) demonstrated that slip severity was significantly correlated with the age of the patient and the duration of symptoms. There is a weakly positive correlation between slip severity and duration of symptoms. (11) Factors that increase physeal stress or decrease resistance to shear forces are associated with SCFE, including obesity and metabolic abnormalities such as hypothyroidism. (5) Compared with white individuals, there is a higher prevalence in black, Hispanic, Polynesian, and Native American individuals. (12)

Presentation

The presentation of SCFE may vary, depending on the severity and stability of the slip. Often, a child will be 10 to 14 years old, will be obese, and will present with a chief complaint of groin/hip or knee pain. The duration of pain may be chronic (>3 weeks) or acute (<3 weeks) in presentation and may be related to a specific event. The pain may be an acute or chronic exacerbation. (13) The average duration of pain before diagnosis with SCFE is 4 to 5 months. (8) Pain may be constant or occur only when weightbearing, and the severity of the pain may differ. Typical pain is unilateral, although bilateral pain/SCFE may be possible and should be evaluated, especially in a younger child (<10 years old) or a child with metabolic abnormalities. (9)(14) Of the 18% to 63% of SCFE cases that are bilateral, only 50% to 60% will present with pain bilaterally. Those with bilateral SCFE presenting with unilateral pain often develop bilateral symptoms within 18 months. (3) Patients may present with painless limp and external rotation of the affected leg. Typically, patients have limited hip range of motion with decreased internal rotation, flexion, and abduction; they may also exhibit obligatory external rotation with passive flexion of the hip (Fig 2). (15) Limited internal rotation is the most commonly seen abnormality on examination. (6)

Patients with stable SCFE will present with the ability to bear weight on the affected extremity, with or without crutches. Patients with an unstable SCFE are unable to bear weight on the affected extremity. Unstable SCFE is associated with a high risk of osteonecrosis, with the literature showing 10% to 60% risk. (16)(17)(18) Sankar et al (16) reported that younger patients with a shorter period of prodromal symptoms and unstable SCFE have a higher rate of avascular necrosis. However, another study by Loder et al showed that slip severity may be correlated with older age and longer duration of symptoms. (11) The increased risk of avascular necrosis with SCFE is directly correlated with the risk of development of early osteoarthrosis. (1) Table 1 summarizes key features that pediatricians should recognize in patients with SCFE.

The average time from the onset of symptoms to diagnosis is approximately 8 weeks. This is due to delay in seeking medical care, initial complaint of knee pain, and insurance status. (19) The average time for a patient to see an orthopedist versus a general provider is 91 days versus 27 days, respectively. (19)

Evaluation

Anteroposterior (AP) and frog-leg lateral radiographs of both hips are of utmost importance when evaluating a patient for SCFE. Knee pain in the immature patient demands critical evaluation of hip motion to rule out hip pathology. The Klein line, the metaphyseal blanch sign of Steel, and epiphysiolysis are helpful radiographic findings to aid diagnosis. (20) Other radiographic measurements may be beyond the scope of this review. The Klein line is evaluated on the AP pelvic radiograph and is a line extended from the lateral cortex of the femoral neck, which should intersect the femoral epiphysis. Epiphyseal location medial to the Klein line is a sign of SCFE. The blanch sign of Steel arises from the overlapping of the posteriorly positioned femoral head in relation to the metaphysis. Epiphysiolysis, which is widening of the growth plate, may be seen compared with the opposite uninvolved hip. (20) Figure 3 shows these measurements and radiologic signs.

Magnetic resonance imaging (MRI) is typically not indicated unless findings are not obvious on radiography and SCFE is still suspected or there is a need to evaluate the contralateral hip in a patient at risk for another slip. (18) In early cases of SCFE, MRI is more sensitive than plain radiographs. (20) Also, MRI may be used to assess bone quality/blood supply of the femoral head in an unstable slip. Computed tomography is typically not needed except for presurgical planning in patients who may require surgical dislocation or osteotomy. (18)

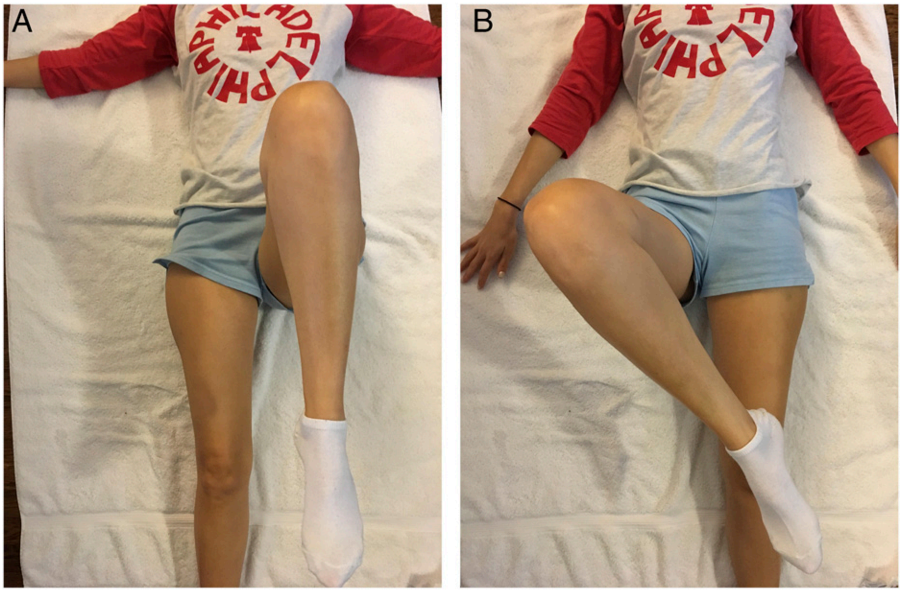


Figure 2. A. The patient's left hip remains in neutral rotation as the hip is flexed to 90°. B. The patient's right hip demonstrates obligatory external rotation: the hip rotates externally as it is flexed to 90°.

TABLE 1. **Key Features of Slipped Capital Femoral Epiphysis that the Pediatrician Can Recognize**

- Age at presentation typically 10 to 14 y (puberty)
- More common in obese patients
- Usually unilateral pain, although may be bilateral
- Typically groin/hip pain, although 15%–23% may present with knee pain
- Walk with limp
- Family history of slipped capital femoral epiphysis
- Obligatory external rotation with flexion
- Can the patient bear weight?
- Males > females (1.5×)

Laboratory values in patients with SCFE should be obtained for children younger than 10 years, children whose weight is less than the 50th percentile, or those with other suspected endocrine abnormalities. Included in the evaluation should be triiodothyronine, thyroxine, and thyrotropin levels to evaluate thyroid function and blood urea nitrogen and creatinine levels to evaluate for osteodystrophy of chronic renal failure. (21)(22)

Treatment and Prognosis

Treatment for SCFE typically involves stabilization of the physis to prevent worsening slippage. Stabilization is primarily performed via percutaneous in situ fixation (Fig 4), with a single screw being placed through the growth plate from the metaphysis into the epiphysis. (3)(13)(18)(23)(24) The decision whether to prophylactically fix the contralateral side has been largely debated. Bilateral slips occur in as many as 63% of patients. (3) The current indications for contralateral fixation are for patients at high risk for slippage, which includes age younger than 10 years, metabolic abnormality, extreme obesity, or unreliable follow-up. (14)(25) Figure 5 shows a child with hypothyroidism who required bilateral SCFE fixation.

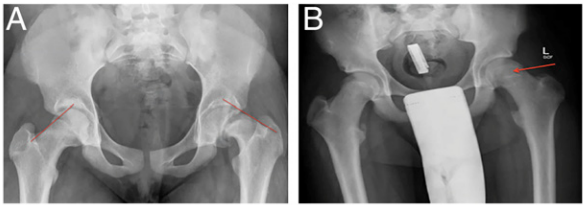


Figure 3. A. Evaluation of a 13-year-old girl with a left-sided slipped capital femoral epiphysis (SCFE). Klein lines are drawn on both sides, illustrating its intersection with the epiphysis on the right side while being lateral to it on the side with the SCFE. B. A 14-year-old boy with left-sided SCFE with metaphyseal blanch sign of Steel showing a crescent-shaped area of increased density over the metaphysis (arrow).

Approximately 61% to 95% of children with endocrine abnormalities had a contralateral slip, which should suggest the need for prophylactic fixation at the time of initial presentation. (21)(26) Severe, chronic slips may also be treated with hip capsule decompression, proximal femoral osteotomies, or epiphyseal reduction/pinning. (23)(27) Despite pinning, there remains a risk of leg length discrepancy, osteonecrosis of the femoral head, osteoarthrosis, and slip progression, although rare. (3)(28)(29) In addition, residual proximal femur deformity may occur, causing impingement due to failure of remodeling. (30)

Patients with SCFE are at increased risk for arthritis; approximately 45% of children with a SCFE are estimated to require a total hip arthroplasty by 50 years after their slip. (31) The femoral neck may deform and cause impingement on the acetabulum, contributing to arthritis. (32) Patients with SCFE may present with progressive loss of hip motion

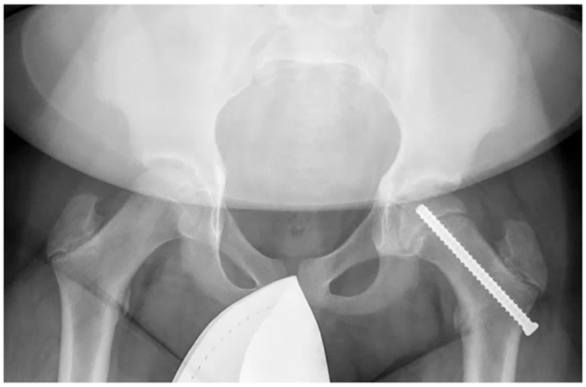


Figure 4. A 13-year-old boy after an in situ single-screw pinning of a left-sided stable slipped capital femoral epiphysis.

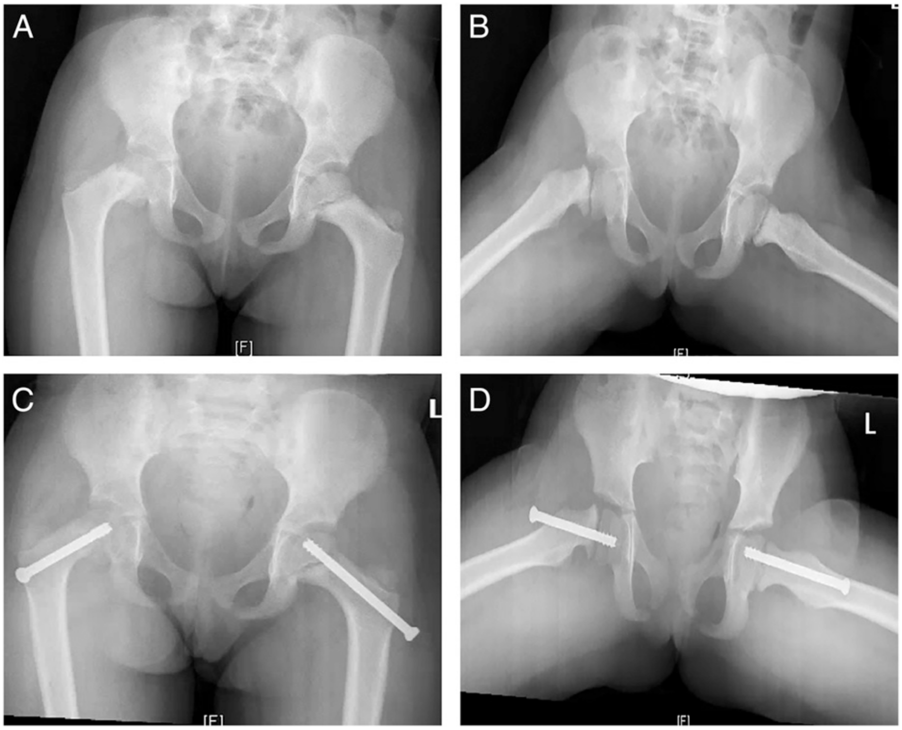


Figure 5. A 6-year-old girl who presented with 3 weeks of groin pain was found to have right hip slipped capital femoral epiphysis. Laboratory findings showed an elevated thyrotropin level, and she was indicated for bilateral hip in situ screw fixation.

due to chondrolysis, or cartilage breakdown. The diagnosis can be confirmed with radiographs showing decreased joint space, and up to 7% of patients may develop this condition, although they tend to do better than patients with SCFE who develop osteonecrosis. (3) Studies have shown that patients who are diagnosed and treated with pinning more than 2 months after initiation of pain tend to have developed more severe slips and thus are at higher risk for complications in the future. (19)

LEGG-CALVÉ-PERTHES DISEASE

Background, Pathophysiology, and Relevant Anatomy

Legg-Calvé-Perthes disease (LCPD) was first described in 1910 by several independent physicians, including Arthur Thornton Legg, Jacques Calvé, Georg Perthes, and Henning Waldenström. (33)(34) This disease constitutes idiopathic osteonecrosis of the femoral capital (head) epiphysis occurring in otherwise healthy young children. (35)(36) Disruption to the femoral head blood supply first results in growth arrest and later a pattern of healing that includes bone resorption, femoral head weakening and flattening (coxa plana), reossification, and, finally, growth resumption. (34) The cause of the initial vascular insult is unknown and the subject of debate; proposed mechanisms include genetic mutations in type II collagen, coagulation abnormalities, repetitive hip loading and extreme flexion as seen with gymnasts, second-hand smoke exposure, venous congestion, and hyperactive behavior. (37)(38)(39)(40)(41)(42)(43)(44)(45)(46)(47)

Epidemiology

The incidence of LCPD is lowest in East Asian populations, ranging from as low as 0.9 per 100,000 up to 21.1 per 100,000 in Liverpool. (34)(48) Patients classically present with symptoms between 4 and 8 years of age but can present from 18 months of age to skeletal maturity. (34)(49) Male to female ratios of 3:1 up to 5:1 have been reported, and bilateral disease occurs in 10% to 15% of patients. (34)(50)

Presentation

Patients usually present with a painless limp for a few weeks to months. Patients may or may not report pain from antecedent trauma. However, pain may or may not be present, and when present, the location can be variable. Due to the innervation of multiple nerves about the hip, pain may be referred to the knee (femoral nerve), medial thigh (obturator nerve), or buttock (sciatic nerve). (33) The diagnosis may, in fact, be delayed when a patient with LCPD notes persistent pain referred to the knee. On physical examination, limited hip abduction and internal rotation (which is best tested with the hip extended) are the most

TABLE 2. Key Features of Legg-Calvé-Perthes Disease that the Pediatrician Can Recognize

• Onset most commonly between ages 4 and 8 y
• Male prevalence (4–5× more likely than females)
• Bilateral involvement in 10%–15% of patients
• Symptoms: pain in the groin, greater trochanter, proximal thigh, or knee; limp exacerbated by activity; possible history of trauma
• Signs: Trendelenburg gait, decreased hip range of motion (especially with abduction and internal rotation)

Adapted from Herring JA, ed (34)

consistent signs of LCPD. (33) Patients may appear to have shortening of the affected extremity in unilateral cases. Patients often have weak quadriceps and hip abductors, with muscle atrophy.

Presentation will vary depending on the age of the patient and stage of LCPD. For example, a young child in an early stage of LCPD may present with a subtle limp and hip pain only during mildly limited range of motion, whereas an older child with a later stage of LCPD or a younger child with severe LCPD may present with a notable limp and inability to bear weight unassisted. The LCPD presentation may be atypical in females, with later age at onset and increased severity of involvement, especially in gymnasts and dancers subject to repetitive microtrauma at the hip. (37) There has been some discrepancy, with other authors reporting similar presentations to males. (51) Table 2 summarizes key features of LCPD that pediatricians can recognize.

Evaluation

An evaluation for LCPD should start with a detailed history and physical examination, as well as radiographs of the pelvis and hips. If the pediatrician is ordering initial imaging, an AP pelvic radiograph with bilateral frog-leg lateral views (hips flexed and abducted) should be obtained. A single hip radiograph is not adequate because comparison with the contralateral hip cannot be made and bilateral disease may be missed. (52) Early radiographic signs include flattening of the femoral head and subchondral sclerosis (Fig 6). (52) Later signs include extrusion of the femoral head laterally such that it is not contained, or covered, by the acetabulum (Fig 7). In most cases, changes in the shape of the femoral head are accompanied by acetabular remodeling. (34)

The classification systems for LCPD are based on radiographic findings. Waldenström described 4 stages characterizing the appearance of the femoral head: initial, fragmentation (Fig 8), reossification, and healed. (34)(50) In another classification described by Stulberg et al, (53) the severity of femoral head deformity at skeletal maturity correlates with the risk of osteoarthritis at mean follow-up of 40 years.

The role of MRI in LCPD diagnosis, management, and prognostication is still evolving. (50) Magnetic resonance imaging has been shown to be more accurate in the early diagnosis of LCPD and to provide earlier and more reliable detail on the extent of femoral head necrosis and proximal femoral physeal involvement as well as the configuration of femoral head and acetabular deformities. (34)(54) More recently, perfusion (Fig 9), diffusion, and delayed gadolinium-enhanced MRI have been used to better understand the pathophysiology and prognosis of this disease. (55)(56)

Legg-Calvé-Perthes disease is a diagnosis of exclusion. Other diseases causing osteonecrosis of the femoral head must first be ruled out before assigning a diagnosis of LCPD. A detailed medical history and family history, as well as medication list, facilitates that. Sickle cell disease, chronic systemic disease such as lupus, chemotherapy, and long-term corticosteroid use can result in osteonecrosis of the femoral head. In addition, radiographic mimickers of LCPD include multiple epiphyseal dysplasia and Gaucher disease, both of which typically affect both hips. (50)(57)

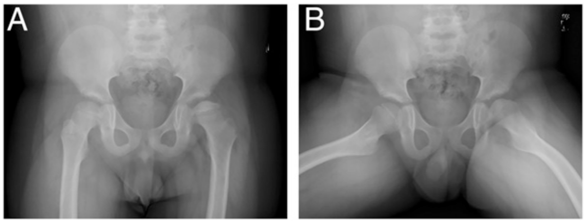


Figure 6. A. An anteroposterior radiograph of the pelvis shows early radiographic signs of Legg-Calvé-Perthes disease in the left hip compared with the right hip, including flattening of the femoral head and subchondral sclerosis. B. These features are again seen on the lateral view.

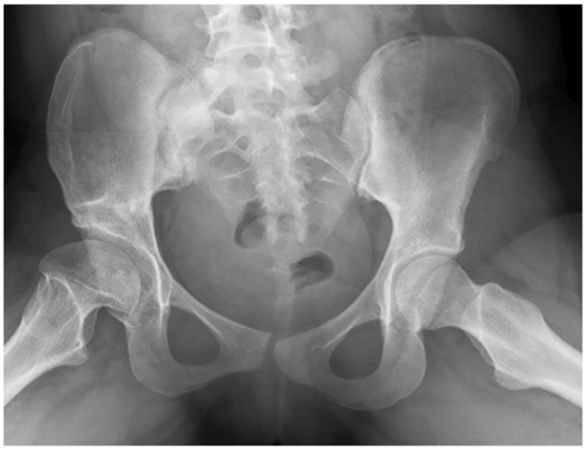


Figure 7. An anteroposterior radiographic of the pelvis shows flattening and extrusion of the right femoral head. Approximately one-third of the lateral aspect of the femoral head is not contained, or covered, by the acetabulum.

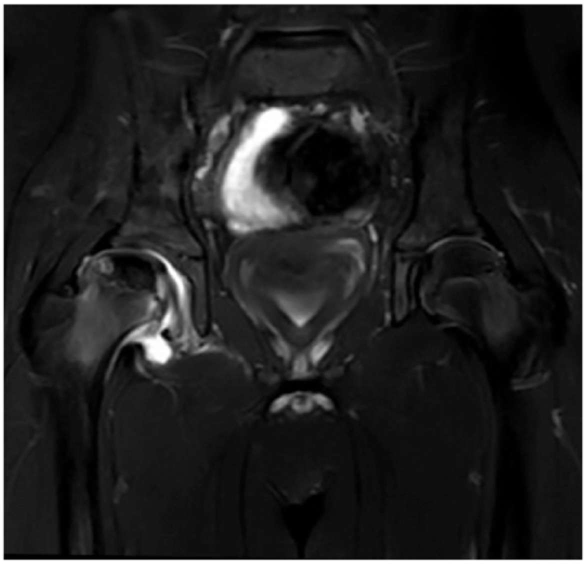


Figure 9. A perfusion-weighted magnetic resonance image of bilateral hips shows changes consistent with Legg-Calvé-Perthes disease of the right hip, including flattening and lateral extrusion of the femoral head relative to the acetabulum, decreased contrast uptake in the right femoral head (dark signal), and a hip joint effusion (bright signal).

Treatment and Prognosis

The best strategy for treating and managing LCPD is early referral to a pediatric orthopedist when there is a suspicion for LCPD. It is important for pediatricians to have a general understanding of the treatment of LCPD to counsel patients and families both when referring patients for suspected LCPD and when following patients long-term who are known to have the disease.

Our knowledge of the etiology and optimal treatment of LCPD continues to evolve, and currently there is no cure. (36) Treatment options vary based on age at presentation, deformity present during active disease, and residual deformity. The goal of treatment is to maintain a spherical femoral head and a concentrically reduced hip through the reossification stage of the disease to prevent eventual degenerative changes while preserving hip range of motion.

The treatment of early disease includes the use of nonsteroidal anti-inflammatory medications, protected weight-bearing, limited physical activity, and physical therapy for range of motion. For the patient who does not improve with these initial conservative measures, surgery to contain the femoral head is the next option, to position the femoral head deeper in the acetabulum (Fig 10), and to improve the coverage on the femoral head. (36)

Multicenter cohort studies out of Norway and the Perthes Study Group have provided the highest level of evidence to date to guide treatment and have shown a difference in outcome depending on patient age at disease onset. (58)(59) A large retrospective study of patients younger than 6 years old indicated that 80% of hips have good results with

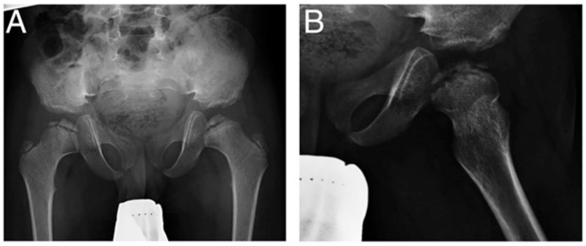


Figure 8. A. An anteroposterior radiograph of the pelvis shows Legg-Calvé-Perthes disease affecting the bilateral hips, with fragmentation of bilateral femoral heads. B. Fragmentation is again seen on a lateral view of the left hip.

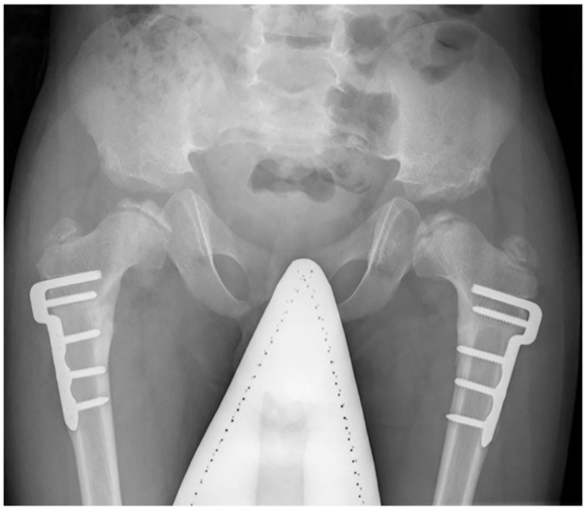


Figure 10. Postoperative anteroposterior pelvic radiograph status post proximal femoral varus osteotomies bilaterally.

TABLE 3. **Distinguishing Slipped Capital Femoral Epiphysis (SCFE) and Legg-Calvé-Perthes Disease (LCPD)**

FEATURE	SCFE	LCPD
Age at onset	Usually pubertal age (10–14 y)	Usually 4–8 y (but can be anywhere from 18 mo to skeletal maturity)
Onset	Variable – acute (<3 wk) versus chronic (>3 wk)	Weeks to months
Previous trauma	Sometimes	Sometimes
Associated diseases	Obesity, endocrinopathy	Coagulopathy, hyperactivity, genetic mutations in type II collagen
Gait	Variable – may be weightbearing (stable) or not able to tolerate weightbearing (unstable)	Usually limping, sometimes with a Trendelenburg gait
Pain	Variable – note that pain can be in the groin, lateral hip, thigh, or referred to the knee	
Range of motion	Restricted – classically, with obligatory external rotation when the hip is flexed	Restricted – classically, loss of internal rotation and abduction
Unilateral or bilateral	18%–63% bilateral	10%–15% bilateral

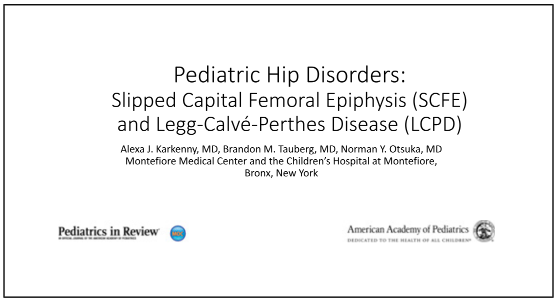
symptomatic or nonsurgical management only. (60) In children younger than 6 years old with greater than 50% femoral head involvement, no significant differences have been seen among treatment with physical therapy, an orthosis, or proximal femur varus osteotomy, whereas children older than 6 years with greater than 50% femoral head involvement showed significantly better results with surgery. (58) Long-term follow-up suggests that more than 50% of patients with LCPD develop disabling arthritis by the sixth decade of life. (61) A 2012 prospective cohort series documenting pain and function in 56 adults who were treated nonoperatively for LCPD reported a 5% rate of total hip replacement at 20-year follow-up. (62)

Table 3 lists the distinguishing features of SCFE and LCPD.

Summary

- Slipped capital femoral epiphysis (SCFE) and Legg-Calvé-Perthes disease (LCPD) may present with classic history and physical examination findings that may aid the pediatrician in making an early diagnosis.
- Pediatricians should refer patients with abnormal physical examination findings, abnormal imaging findings, or persistent hip, knee, or groin pain despite normal imaging findings to a pediatric orthopedist.
- Based on strong research evidence, there are adult consequences of SCFE and LCPD, including chondrolysis and secondary osteoarthritis resulting in a need for total hip arthroplasty. (3)(14)(25)(61)(62)
- Treatment of SCFE and LCPD remains under debate. (3)

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/9/454.supplemental.



Pediatric Hip Disorders:
Slipped Capital Femoral Epiphysis (SCFE)
and Legg-Calvé-Perthes Disease (LCPD)
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1. A 13-year-old boy with a medical history of mild persistent asthma presents to the pediatrician's office for evaluation of a 6-week history of right thigh and knee pain. He plays linebacker on the middle school football team but has not been to practice this week due to worsening discomfort. He denies fever, recent illnesses, or trauma. His medications include inhaled albuterol and fluticasone. His surgical history is significant for a right tibial fracture at 3 years of age. Family history is significant for osteoarthritis in the maternal grandmother. On physical examination he is noted to have a body mass index of 28 and an antalgic gait. He lies on the bed with his right leg externally rotated and has decreased range of motion with internal rotation of the right hip. Which of the following risk factors most contributed to his condition?
    - A. Family history of osteoarthritis.
    - B. Inhaled corticosteroid use.
    - C. Obesity.
    - D. Participation in contact sports.
    - E. Previous right tibial fracture.
2. You advise the patient in question 1 to refrain from weightbearing and order anteroposterior (AP) and frog-leg lateral radiographs of the hips. In addition, you refer the patient to a pediatric orthopedic surgeon for immediate evaluation. Which of the following findings do you expect to see on the AP and frog-leg lateral radiographs?
    - A. Deformity of the acetabulum.
    - B. Flattening of the femoral head.
    - C. Focal femoral lytic lesion.
    - D. Narrowing of the femoral growth plate.
    - E. Posterior dislocation of the femoral epiphysis.
3. A 14-year-old obese girl with a medical history of hypothyroidism is diagnosed as having slipped capital femoral epiphysis and undergoes percutaneous in situ fixation of the right femoral head and prophylactic fixation of the contralateral hip. Which of the following is the most likely long-term complication of her condition?
    - A. Growth failure.
    - B. Hemarthrosis.
    - C. Osteoarthritis.
    - D. Osteomyelitis.
    - E. Recurrent fractures.
4. A 6-year-old boy is brought to the emergency department for evaluation of left hip pain. The pain began initially 2 months ago after a fall at school and resolved spontaneously. Today he states that the pain has worsened over the past month and is localized to the left hip and knee. His mother also states that he began limping 1 week ago. On physical examination, he has limited hip abduction and internal rotation and mild atrophy of the quadriceps. Both AP and frog-leg lateral radiographs demonstrate flattening of the femoral head and subchondral sclerosis. Which of the following best describes the pathophysiology of this patient's condition?
    - A. Displacement of the proximal femoral epiphysis.
    - B. Disruption of the blood supply to the femoral head.
    - C. Fracture involving the femoral epiphysis, growth plate, and metaphysis.
    - D. Inflammatory bony destruction caused by chronic infection.
    - E. Malignant invasion leading to abnormal osteoid formation.

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5. A 5-year-old boy presents to the pediatric orthopedic surgeon's office for evaluation of a 2-month history of intermittent right hip pain and a limp. He was seen by his primary care physician last week, who ordered hip radiographs, which demonstrated findings consistent with avascular necrosis of the femoral head. On physical examination, the patient is observed to have an asymmetrical gait and pain with internal rotation of the right hip. Which of the following is the next best step in management?
   - A. Biopsy of the femoral head.
   - B. Broad spectrum antibiotic therapy.
   - C. Nonsteroidal anti-inflammatory medications and physical therapy.
   - D. Percutaneous in situ fixation.
   - E. Surgical reconstruction of the acetabulum.

Index of Suspicion

1 Recurrent Pneumonia in a 15-year-old Girl

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Jichlinski, Kilaikode, and Koumbourlis have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 15-year-old girl presents with a history of back pain, chills, and shortness of breath of 1 day's duration. On examination she is afebrile and well appearing despite mild tachypnea (respiratory rate of 24 breaths/min). Oxyhemoglobin saturation is normal (95%–100%) on room air. On auscultation she has absent sounds in the left lower lung (LLL) fields but normal breath sounds on the right. Initial laboratory tests show a white blood cell count of 13,050/μL (13.05×10^9/L), a hemoglobin level of 14.1 g/dL (141 g/L), a hematocrit value of 40.5%, and a platelet count of $226 \times 10^3/\mu$L (226×10^9/L). A basic metabolic panel is normal, and lactate dehydrogenase and uric acid levels are within their respective reference ranges. The C-reactive protein level is elevated at 8.56 mg/L (81.53 nmol/L). A chest radiograph (CXR) reveals a large area of consolidative opacity in the left hemithorax (compatible with pneumonia and/or atelectasis) and probable pleural effusion (Fig 1).

Her medical history is notable for a diagnosis of mild asthma and an episode of pneumonia 18 months before presentation, diagnosed clinically without CXR and treated with antibiotics as an outpatient. She was also admitted to the hospital twice with a diagnosis of LLL pneumonia and pleural effusion 7 and 6 months before this admission. She responded promptly to antibiotic therapy, and no other intervention was taken. At a follow-up appointment after the second hospitalization she was well appearing but had decreased breath sounds on the left base. Her pulmonary function test result was consistent with mild to moderate restrictive lung defect. A CXR revealed a residual density in the LLL that was thought to represent the gradual clearing of the previous pneumonia.

The patient is admitted to the hospital for further evaluation and treatment with intravenous antibiotics. Further imaging reveals the diagnosis.

DISCUSSION

Recurrent pneumonia in children is always a cause of concern because it often results from underlying conditions or anatomical abnormalities that can be summarized as follows: 1) immunodeficiencies (genetic or acquired), 2) conditions that promote the accumulation of mucus into the lungs (eg, poorly controlled asthma or cystic fibrosis), 3) conditions that impair the clearance of mucus from the airways

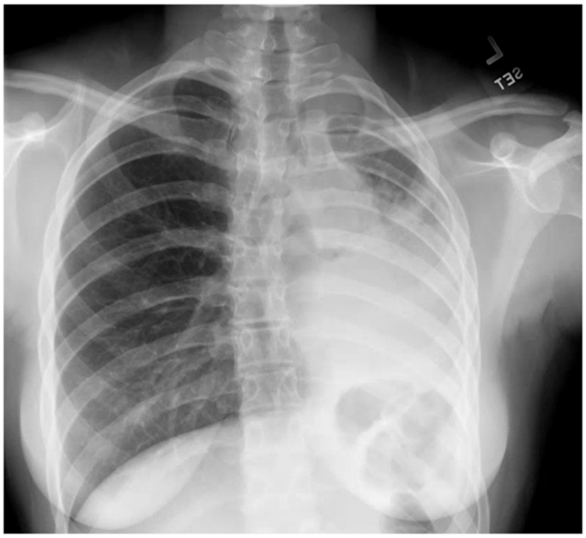

Figure 1. Chest radiograph on hospital admission.

(eg, primary ciliary dyskinesia or tracheobronchomalacia), 4) structural abnormalities of the lungs (eg, cystic pulmonary airway malformations), and 5) indolent infections (eg, tuberculosis).

The patient's CXRs all showed partial consolidation of the LLL that had improved during her follow-up appointment. Recurrent pneumonia in the same location is usually associated with an anatomical abnormality and raises suspicion for pulmonary sequestration.

Although the patient was admitted to the hospital 3 times with the diagnosis of pneumonia with pleural effusion, there were elements of her presentation that made a primary diagnosis of infectious pneumonia less likely. Specifically, she did not have high fever and leukocytosis, and despite the impressive consolidation on CXR she was not hypoxemic, suggesting that there was no acute, severe ventilation/perfusion mismatching.

Chest ultrasonography showed only a small pleural effusion and evidence of collapse versus consolidation of most of the left lung. A computed tomographic (CT) scan of the chest revealed a mass lesion at the origin of the left main bronchus, consolidation and collapse of the left lung, a small circumferential pleural effusion, and marked leftward mediastinal shift (Fig 2).

Flexible bronchoscopy revealed a large, irregular, lobulated, "cauliflower-like" mass at the lower left wall of the trachea that was obstructing the takeoff of the left mainstem bronchus and part of the carina. The mass was soft and fleshy (Fig 3). The right mainstem bronchus and its lobar and segmental bronchii were patent. Multiple forcep biopsies were obtained. Pathologic evaluation revealed large cells with abundant cytoplasm that stained positive for vimentin and S100, consistent with a benign granular cell tumor. Bronchial washings were obtained and were negative for bacterial, fungal, or viral pathogens. The tuberculin purified protein derivative test result was negative.

The Condition

Granular cell tumors (GCTs) originate from Schwann cells, although the exact pathology leading to their formation is unknown. (1) Lung GCTs are extremely rare, accounting for less than 10% of all GCTs, the incidence of which has been estimated to be 5 cases per million person-years in the general population. The incidence in the pediatric population is significantly lower. (2)(3) Pulmonary GCTs tend to be found in the larger airways at bifurcation sites, with a higher number of reported pediatric cases originating in the larynx. (4) Although most often benign, several cases of malignant GCTs have been reported in adults. (5)

Pathologically, GCTs are composed of polygonal or ovoid cells with large eosinophilic, granular cytoplasms. The nuclei are often small, hyperchromatic, and eccentric, with absent mitosis. S-100 protein, neuron-specific enolase, CD56, and chromogranin are expressed in pulmonary GCTs, consistent with the pathology reported in the present case. (6)

The differential diagnosis for bronchial and tracheal masses is large and includes pulmonary carcinomas, hemangiomas, inflammatory pseudotumors, rhabdomyosarcomas, neurofibromas, and squamous cell carcinomas. (1)(7) Note that pneumonia and/or atelectasis may be the presenting symptom of an endobronchial lesion because the intraluminal mass prevents the clearance of secretions from the airways, thus predisposing the patient to infection. The fact that patients clinically improve with antibiotic therapy often delays diagnosis of the tumor.

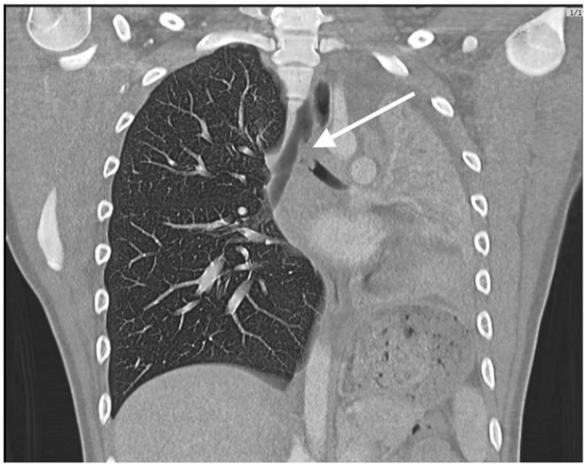

Figure 2. Computed tomographic scan of the chest revealing a filling defect in the left mainstem bronchus, collapse of the left lung, and compensatory hyperinflation of the right lung.

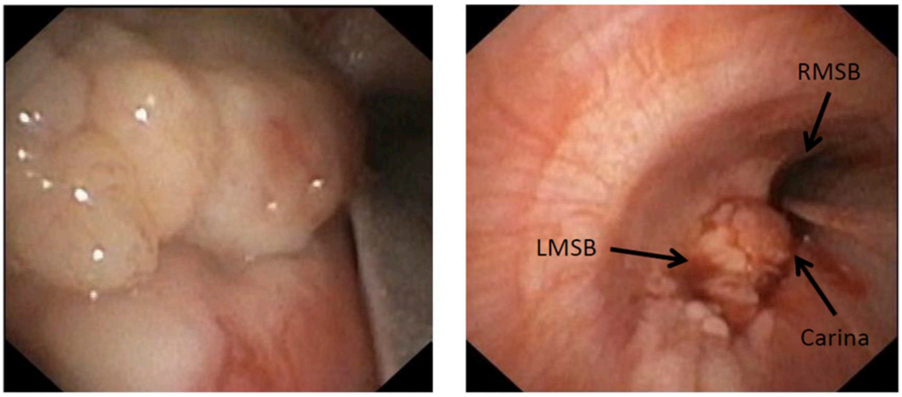

Figure 3. Bronchoscopic appearance of the tumor obstructing the takeoff of the left mainstem bronchus (LMSB), the open right mainstem bronchus (RMSB), and the carina.

Management and Prognosis

Management of GCTs is still debated because few cases have been reported. The tumors do not respond to chemotherapy or radiotherapy, so surgical resection is always necessary. (6) The size of tumors and invasion of the tracheobronchial wall play a role in guiding surgical management; larger, more invasive tumors require complete resection of the lung via thoracic surgery. (8)(9)

Some authors have advocated for endoscopic removal of smaller intraluminal lesions with close follow-up and monitoring for recurrence. (1)(10)(11) Although endoscopy may not always allow the complete resection of the tumor, it is less invasive than pneumonectomy and has significantly lower morbidity. Most importantly, there has never been documented malignancy of a GCT in the pediatric age group, and recurrence due to incomplete resection is rare (0%–12%). (1)(5) However, it must be kept in mind that given the paucity of cases, true recurrence rates remain unknown.

Patient Course

The patient's tachypnea and back pain improved with intravenous antibiotic therapy, and she was discharged on oral antibiotics. The tumor was excised a few weeks later by endoscopic sleeve resection, obviating the need for lobar or total lung resection. The lung fully reexpanded postoperatively.

Conclusion

Our patient's presentation illustrates the need to thoroughly investigate any recurrent or persistent "pneumonia." Because no CT scan or bronchoscopy was performed during the first 2 hospital admissions, we cannot be absolutely certain that the tumor was present at the first admission. However, the lack of hypoxemia in the setting of absent breath sounds in the LLL field and severe atelectasis on CXRs suggest a slowly growing tumor that was gradually obstructing the LLL, allowing the diversion of the blood flow to the right lung and avoiding the development of ventilation/perfusion mismatching. It is likely that there was also a superimposed infectious process present because the patient clinically improved with the administration of antibiotics during all her hospital admissions. Superimposed bacterial infections are common in endobronchial lesions that impair the clearance of secretions and predispose the affected lung to colonization with bacterial organisms that may cause bacterial bronchitis and/or pneumonia.

Uncomplicated community-acquired pneumonia can be diagnosed and treated on the basis of the clinical presentation and physical findings alone, without the need for CXR. However, when the patient has recurrent episodes, it is virtually impossible to determine whether it is a recurrence of the same pneumonia or a new and unrelated episode. In addition, the radiographic findings of pneumonia may persist for weeks or even months after a single episode. Thus, it is imperative for primary care physicians to follow patients closely and monitor until there is complete clinical resolution. The diagnosis of 2 or more episodes of pneumonia should include CXR and a follow-up CXR several weeks after the clinical recovery to document resolution.

Recurrent or persistent "pneumonia" requires further investigation. A CT scan of the chest with contrast is a reasonable starting point. Suspected pleural effusions should be evaluated with ultrasonography to detect and quantify the presence of free fluid or loculations in the pleural cavity. Flexible bronchoscopy should be performed when an obstructing lesion is suspected and/or if bronchoalveolar lavage is needed to identify pathogens.

Lessons for the Clinician

- Recurrent pneumonia, especially in the same location, should raise suspicion for an underlying condition predisposing the patient to the pneumonia, and it should be thoroughly investigated.
- Radiographic findings that are disproportionately severe relative to the clinical presentation suggest a chronic, slowly evolving process as opposed to an acute process that is usually associated with substantial distress and hypoxemia.
- Flexible bronchoscopy should be considered when airway obstruction (either from an intraluminal mass or due to external compression or malacia) is suspected.
- Parapneumonic effusions may be difficult to distinguish from atelectasis/consolidation if there is no free-flowing fluid that would layer in a decubitus position. Thus, their presence should be confirmed by chest ultrasonography and/or computed tomography with contrast.

Note. This case is based on a poster presentation by Drs Kilaikode, Jichlinski, and Koumbourlis at the American Thoracic Society International Conference; Washington, DC; May 22, 2017. Poster No. 8842.

References for this article are at http://pedsinreview.aappublications.org/content/39/9/464.

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2

Fever, Neck Pain, and Back Pain in a 16-year-old Boy

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AUTHOR DISCLOSURE Drs Trauernicht, Bharill, Panko, and Friehling have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A previously healthy 16-year-old boy presents to the emergency department with 1 day of headache, neck pain, and fever. Three nights previously after soccer practice he had acute, severe low back pain, now resolved. He has otherwise been well, without nausea, vomiting, or vision changes. His immunizations are up to date. He has no known sick contacts. He does not take medications. He recently went camping but does not recall any insect bites.

Physical examination reveals an uncomfortable boy lying very still. His temperature is 100.9°F (38.3°C), heart rate is 91 beats/min, respiratory rate is 18 breaths/min, and blood pressure is 113/60 mm Hg. He has optic disc edema and limited range of motion of the neck with pain that radiates down his spine on flexion. The remainder of his physical examination findings are normal.

Laboratory evaluation reveals a normal complete blood cell count, basic metabolic panel, sedimentation rate, and urinalysis results. His C-reactive protein level is elevated at 3.85 mg/dL (38.5 mg/L). Findings from computed tomography of the head are normal. A lumbar puncture is obtained. Cerebrospinal fluid (CSF) is grossly bloody and xanthochromic, with 2,683 white blood cells/μL (× 10^9/L) (85% neutrophils, 5% lymphocytes, 10% monocytes), 28,624 red blood cells (RBCs)/μL (× 10^9/L), a low glucose level of 24 mg/dL (1.33 mmol/L), and an elevated protein level of 130 g/dL (1,300 g/L).

The patient is started on antibiotic therapy. His neck pain and fever resolve, but his low back pain returns and persists. The diagnosis is made after further evaluation.

DISCUSSION

This boy's presentation with fever and meningismus was highly concerning for bacterial meningitis. A CSF pleocytosis with neutrophilic predominance and hypoglycorrhachia (low glucose content in the CSF) supported this diagnosis. The elevated RBC count in the CSF was attributed to a traumatic tap. However, the patient continued to have low back, buttock, and bilateral posterior lower extremity pain. Subsequent physical examination demonstrated intact strength in bilateral lower extremities but significant discomfort with flexion at the waist and with bilateral straight-leg raise. This prompted us to perform magnetic resonance imaging (MRI) of the lumbar spine, which revealed an intraspinal mass on the cauda equina extending to the conus medullaris, most consistent with a hemorrhagic myxopapillary ependymoma.

The Condition

Spinal cord and cauda equina neoplasms account for 3% of all primary brain and central nervous system tumors in pediatric and adolescent patients, and of those, ependymomas are the most common at 22%. (1) Conversely, of primary childhood ependymomas, only 13% are located in the spinal cord. (2) Myxopapillary ependymomas have a slight male predominance and more often occur in white adolescent males. (3) Myxopapillary ependymomas usually involve the filum terminale, cauda equina, or conus medullaris, although they can have thoracic involvement and can present with leptomeningeal disseminated disease. (3) Relapse and later onset of leptomeningeal disseminated disease are common.

Diagnosis

Back pain in children and adolescents is usually due to a musculoskeletal etiology. As was the case for our patient, a heightened suspicion for pathologic etiologies of back pain should occur when a child or adolescent endorses back pain that is persistent, severe, of a radicular distribution, or worse at night. In patients who are ultimately diagnosed as having myxopapillary ependymoma of the spinal cord, motor, sensory, sphincter, urinary, or gait abnormalities may occur. However, the absence of these symptoms does not rule out the possibility of a spinal cord tumor. Back pain initially can be subacute or nonspecific until compression of the spinal cord occurs, as these tumors are slow growing and are usually well circumscribed. An MRI of the brain and spinal cord is required for initial tumor staging.

Patients with myxopapillary ependymoma of the spinal cord may also present with signs of meningeal irritation, elevated intracranial pressure, and papilledema. If CSF analysis is pursued, it can reveal elevated protein and RBC values, xanthochromia, and hypoglycorrhachia. (4) Cytology is often negative, as was seen in our patient. These results may be confused with meningitis if imaging is not obtained first. Due to the low diagnostic yield of CSF analysis, lumbar puncture is not recommended unless central nervous system dissemination is suspected.

Management

No published therapeutic guidelines exist for treatment of spinal cord ependymoma in children due to a paucity of long-term outcome data. (5) The outcome in children generally depends on the grade and extent of tumor involvement in the spinal cord, which determines whether gross total resection (GTR) is possible. The GTR yields the best long-term survival with the lowest incidence of tumor recurrence. Survival in patients who underwent GTR is 97% at 5 years and 95% at 10 years based on some pediatric studies. (5) In comparison, pediatric patients who underwent subtotal resection plus radiation therapy had 5-year overall survival of 91%. (5)

The role of adjunctive radiotherapy after GTR is unclear. Some studies have demonstrated potential impact in recurrence-free survival rates given that the recurrence of local and metastatic disease is higher in children than in adults with myxopapillary ependymoma. (1) If only subtotal resection can be achieved due to tumor complexity and adherence to the spinal cord, there are 2 options: adjuvant radiotherapy or watchful waiting with close surveillance for tumor recurrence. Chemotherapy is not used in initial treatment of myxopapillary ependymoma.

The preferred method of postoperative surveillance for all patients is local MRI. (2) Our patient will be monitored with a lumbar spine MRI every 3 to 4 months for the first 2 years, every 6 months for 3 to 5 years, and yearly thereafter.

Patient Course

Our patient underwent successful GTR and had no evidence of residual or recurrent tumor on surveillance MRIs 3 and 6 months later. He described left lower extremity paresthesia in the immediate postoperative period but has intact strength and sensation on examination. He has not received any adjuvant chemotherapy or radiation.

Lessons for the Clinician

- Persistent, severe back pain in a healthy adolescent is not normal and requires evaluation.
- Although cerebrospinal fluid pleocytosis is most commonly due to meningitis, inflammatory and oncologic processes should be included in the differential diagnosis, particularly when the clinical presentation is atypical.
- Motor, sensory, sphincter, urinary, or gait abnormalities should not be considered essential to diagnosis of a spinal cord ependymoma.

References for this article are at http://pedsinreview.aappublications.org/content/39/9/468.

Index of Suspicion

3 A 17-year-old Boy with 6 Weeks of Left Neck Swelling

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AUTHOR DISCLOSURE Drs Almaghraby, Chason, and Banigan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 17-year-old boy with a history of autism spectrum disorder, small lymphatic malformation on the scalp, and scoliosis presents to the emergency department with a 6-week history of left lower neck swelling. He was initially evaluated by his primary care physician and completed a 10-day course of clindamycin for presumed lymphangitis. The swelling initially improved, but within a few days of stopping clindamycin, the swelling worsened again. He was restarted on clindamycin, and given the recurrence of symptoms, a computed tomographic scan of the neck and chest was obtained (Fig 1). Findings showed a large, nonenhancing, low-density mass extending from the left neck down into the superior mediastinum and left upper thorax with mild rightward displacement of cervical and mediastinal structures and encasement of the left subclavian artery. No airway compression or narrowing was noted. He was transferred to our institution for further evaluation with concern for a possible neoplastic process.

In the emergency department he is afebrile, with a heart rate of 90 beats/min, a respiratory rate of 18 breaths/min, and blood pressure of 115/73 mm Hg. Physical examination shows an alert and oriented patient in no respiratory distress. There is notable swelling over the left anterior neck immediately above the clavicle measuring 3 × 4 cm. It is fixed, hard, and nontender to the touch. There is no overlying erythema or warmth. No cervical or axillary lymphadenopathy is noted.

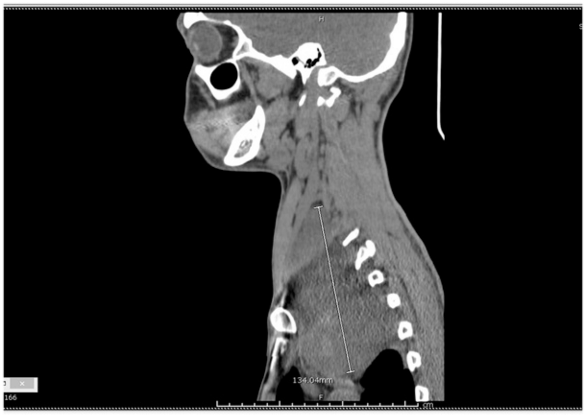

Figure 1. Chest computed tomographic scan showing the craniocaudal length (13.4 cm) of the plexiform neurofibroma.

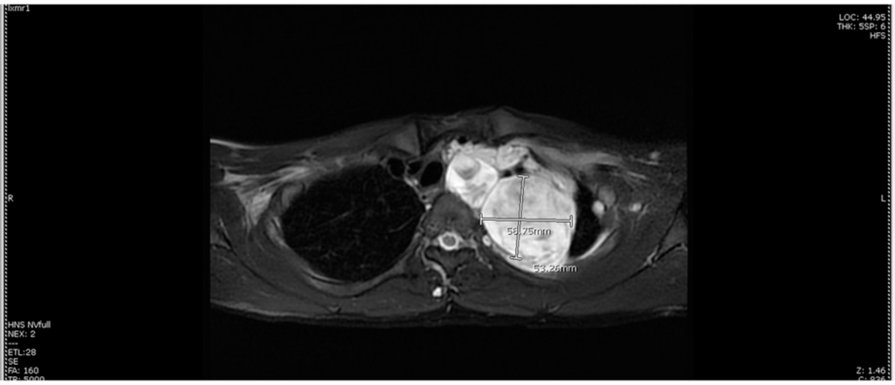

Figure 2. Chest magnetic resonance image in the transverse view showing the width (5.3 cm) and depth (5.9 cm) of the plexiform neurofibroma.

Skin examination reveals multiple café-au-lait spots on the right upper back (15 × 10 mm), left lower abdomen (30 × 15 mm), and right anterior neck (10 × 5 mm). A soft mobile nodule is palpated on the right parieto-occipital scalp that the parents refer to as his small lymphatic malformation. No axial or inguinal freckling is noted. Eye examination shows multiple slightly raised, brown, hyperpigmented lesions on both irides.

Results of his complete blood cell count, electrolytes, glucose, amylase, lipase, liver enzymes, coagulation studies, uric acid, and lactate dehydrogenase were all normal. Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, were also within normal limits. Peripheral blood smear showed no abnormalities. Further imaging and genetic testing revealed the diagnosis.

DISCUSSION

Magnetic resonance imaging of the neck and chest was performed and showed a large multiloculated solid mass with restricted diffusion and signal characteristics extending from the C4-C7 neural foramina down into the superior mediastinum partially encasing the aortic arch (Fig 2). Findings seemed to be most consistent with a large plexiform neurofibroma. Additional T2 hyperintense foci were noted in the anterior chest wall and the medial aspect of bilateral arms consistent with small neurofibromas. A biopsy of the mass was subsequently performed by interventional radiology and is consistent with intraneural neurofibromas (Figs 3 and 4). An ophthalmology evaluation confirmed the presence of Lisch nodules. Given the findings of café-au-lait spots, Lisch nodules, and a plexiform neurofibroma, he met the diagnostic criteria for neurofibromatosis type 1 (NF1). Genetic testing revealed a pathogenic mutation in the *NF1* gene designated c.5923delA (p. Ile1975TyrfsTer18). More specifically, there is a deletion of an "A" nucleotide in the 5923rd position of the gene resulting in a frameshift and the creation of a premature stop codon with truncation of the protein product, which confirms the diagnosis. The patient's mother and sibling tested negative

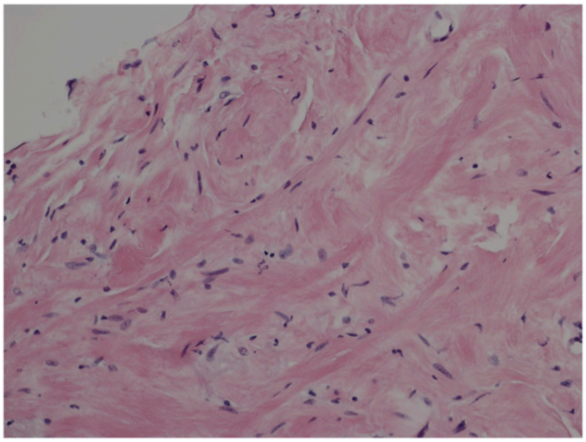

Figure 3. Microscopic examination with hematoxylin and eosin stain showing minimally cellular sample with intertwining fiber bands not arranged in parallel form.

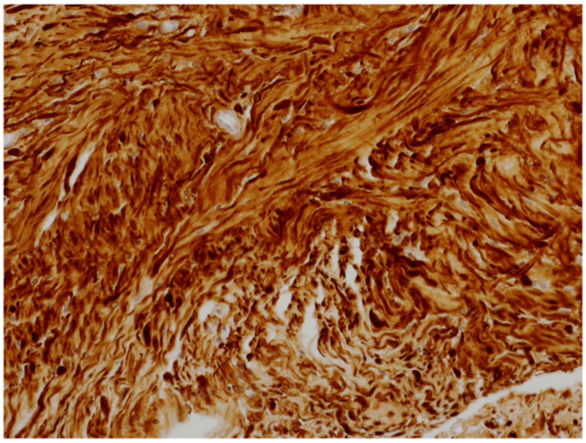

Figure 4. Microscopic examination with S100 stain showing a fascicular appearance and a rare ganglion cell.

for NF1. Because the plexiform neurofibroma encases numerous vascular structures, including the aortic arch and the left subclavian and vertebral arteries, the mass was deemed inoperable. Given the size of the mass with increased risk of malignant transformation, he was started on a clinical trial with selumetinib (MEK inhibitor).

Plexiform neurofibromas are benign, slow-growing tumors that mostly start developing at puberty. They can be seen in 20% to 50% of patients with NF1. Their size can increase by 20% per year. (1) Selumetinib is an oral selective inhibitor of MEK 1 and 2 that was shown in clinical trials to induce noticeable tumor regression. It is usually administered twice a day in a 28-day cycle. The maximum response of selumetinib seems to be more pronounced after 20 cycles by decreasing the tumor volume by up to 31%. (2) In our patient, selumetinib induced a decrease in the tumor volume by 15% after 7 cycles, but, unfortunately, it had to be discounted due to severe pancreatitis.

Lessons for the Clinician

- If 6 or more café-au-lait spots (measuring ≥0.5 cm in a child or ≥1.5 cm in a postpubertal adolescent) are identified on examination, clinicians must be diligent and look for a second defining feature that may confirm the diagnosis of neurofibromatosis type 1.
- Plexiform neurofibromas can grow internally and not be recognized until they cause symptomatic impingement on a surrounding structure.
- Patients with plexiform neurofibromas that are deemed inoperable and at risk for malignant transformation are now being enrolled in clinical trials with investigational drugs, including selumetinib (MEK inhibitor).

References for this article are at http://pedsinreview.aappublications.org/content/39/9/470.

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4

Persistent Lung Lesion in a 6-year old Boy with Sickle Cell Disease

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AUTHOR DISCLOSURE Drs Zaidi and Henry have disclosed no financial relationships relevant to this article. Dr Callaghan has disclosed that he is involved in a Pfizer-funded investigator-initiated research study of sickle cell disease; that he is site principal investigator for 4 studies by Genentech and for studies by Sancillo and Global Blood Therapeutics; that he receives honoraria from Bayer, Shire, Novo Nordisk, and Genentech for speaking engagements; that he has participated in advisory boards for Shire, Genentech, Pfizer, Bayer, and Grifols; and that he owns stock in Alnylam. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 6-year-old boy with sickle cell disease (hemoglobin SS), who is on a long-term exchange transfusion program for repeated splenic sequestration and abnormal transcranial Doppler findings, presents to the emergency department with upper respiratory symptoms and a sore throat. On physical examination he appears well. His temperature is 99.3°F (37.4°C), heart rate is 100 beats/min, respiratory rate is 18 breaths/min, blood pressure is 110/65 mm Hg, and oxygen saturation is 100% on room air. A chest radiograph shows a lesion in the left upper lobe (Fig 1), thought to be round pneumonia, and the child is started on cefepime and azithromycin. It is noted that a very similar lesion was seen on radiography at the time of a previous hospital admission for upper respiratory infection 6 months earlier. Due to persistence of the opacity, a chest computed tomographic scan is performed and reveals a well-circumscribed round mass measuring 4 × 4 × 4 cm in the left hilum, centered at the bifurcation of the upper and lower bronchi (Fig 2). The mass is solid, homogeneous, and without calcification. A left thoracotomy and complete excision of the mass is completed. The specimen is sent to the pathology laboratory, and this leads to the eventual diagnosis.

DISCUSSION

Differential Diagnosis

Based on the history, physical examination, and radiographic findings, it is ascertained that this child has a round chest mass. This child was initially admitted to the hospital with bacterial pneumonia with focal consolidation. Pulmonary consolidations in children tend to be spherical, and the etiology of these "round pneumonias" is often *Streptococcus pneumoniae*. This would be the most common scenario in a healthy 6-year-old boy. However, these consolidations usually resolve rapidly after initiation of antibiotics and should not persist over several months.

In a child with sickle cell disease, one must account for the possibility of lesions of extramedullary hematopoiesis. Extramedullary hematopoiesis is the growth of hematopoietic cells in areas other than the bone marrow, and it can occur in settings of bone marrow replacement or hemolytic anemias. Although most frequently found in the liver, spleen, and lymph nodes, it can be found in the thymus, kidney, and retroperitoneum. Thoracic extramedullary hematopoiesis is infrequent but has been described in sickle cell disease. (1)

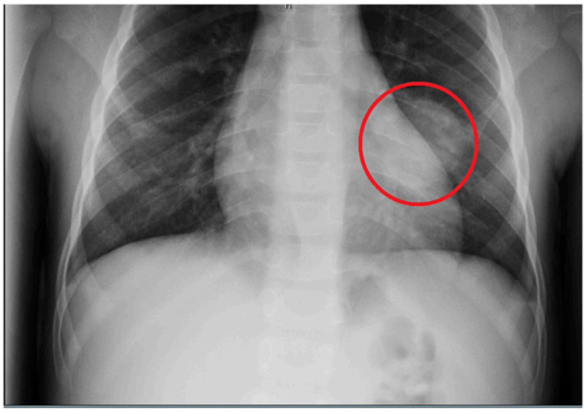

Figure 1. Chest radiograph depicting the presence of a focal rounded opacity overlying the left mid-lung measuring approximately 4.5 cm (red circle).

Finally, the exclusion of a neoplasm is mandated on the care team. This is generally achieved via biopsy and pathologic diagnosis. Our patient was found to have Hodgkin lymphoma on biopsy.

The Condition and Diagnosis

Hodgkin lymphoma accounts for approximately 7% of childhood cancers and 1% of childhood cancer deaths in the United States. (2) The evaluation of Hodgkin lymphoma begins with a thorough medical history, including assessing for the presence of "B" symptoms, including fever, weight loss, and drenching night sweats. Although not the case in our patient, a good history is vital in identifying the presence of potentially life-threatening complications, such as superior mediastinal or superior vena cava syndrome (orthopnea, swelling of the face or limb, etc), in patients with lymphoma. The most frequently found physical finding in these patients is lymphadenopathy. A laboratory profile can reveal abnormalities in the complete blood cell count, including neutrophilic leukocytosis, lymphopenia/lymphocytosis, eosinophilia, monocytosis, and anemia. The biochemical profile can reveal an elevated lactate dehydrogenase level, a low albumin level, and elevated markers of inflammation, including erythrocyte sedimentation rate, C-reactive protein, copper, and ferritin. It is important to remain cognizant of the possibility of lymphoma, even in the absence of any laboratory abnormalities, particularly in children who may have low-stage disease.

Imaging with computed tomography of the neck, chest, or abdomen may reveal lymph node or organ involvement. The metabolic activity of lymph nodes and extralymphatic organs can be evaluated by 18-fluoro-deoxyglucose positron emission tomography. Definitively, a lymph node or bone marrow biopsy is necessary to provide histologic confirmation of Hodgkin lymphoma.

The staging of Hodgkin lymphoma is based on the presence of involved lymph nodes or organs on one or both sides of the diaphragm. The presence or lack of B symptoms, extranodal disease, and bulky disease can also affect staging.

Although the histologic classification of Hodgkin lymphoma is beyond the scope of this article, broadly, the World Health Organization classifies 2 major subtypes of Hodgkin lymphoma: classical and nodular lymphocyte predominant. Classical Hodgkin lymphoma includes nodular sclerosis, mixed-cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes. Children with nodular lymphocyte-predominant or mixed-cellularity subtypes are more likely to have early-stage disease and to lack systemic symptoms.

Management

Contemporary combined-modality therapy has resulted in excellent event-free survival rates in children with Hodgkin lymphoma. The regimen of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) serves as the backbone in current Children's Oncology Group Hodgkin lymphoma protocols. Radiotherapy is used as an adjunct for a subgroup of children with residual metabolically active disease or bulk mediastinal disease.

Individualized response-based therapy has allowed for both continued excellent survival rates as well as reduction of therapy-related toxicity, particularly long-term. This approach assesses disease response to chemotherapy to determine the need for intensification of treatment. Future efforts will focus on integration of new agents for further

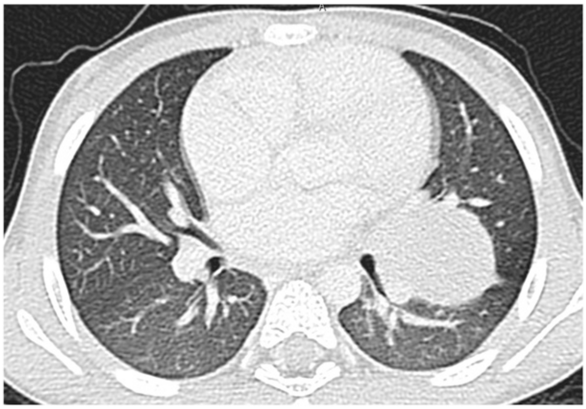

Figure 2. Computed tomographic scan of the chest showing a sharply marginated, well-circumscribed round mass measuring approximately 3.7 × 3.8 × 3.3 cm in the anteroposterior, transverse, and cranial caudal dimensions, respectively, seen in the left hilum, centered at the bifurcation of the upper and lower bronchi. The mass appears solid and homogeneous in attenuation, without evidence of enhancement, necrosis, or internal calcifications.

reduction of late effects, as well as identification of biomarkers for risk stratification.

Lessons for the Clinician

- Acute chest syndrome and pneumonia are common diagnoses in sickle cell disease, but other etiologies must always be considered when caring for this group of children.
- Hodgkin lymphoma is a common pediatric cancer that can be effectively treated with combined-modality treatment regimens that include chemotherapy and radiotherapy.

References for this article are at http://pedsinreview.aappublications.org/content/39/9/473.

Invasive Aspergillosis

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AUTHOR DISCLOSURE Drs Darling and Milder have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Disease Society of America. Patterson TF, Thompson GR III, Denning DW, et al. *Clin Infect Dis.* 2016;63(4): e1–e60

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***Aspergillus* Species,** Patterson TF, Bennet JE, Bolin R, Blaser MJ, Mandell GL. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2010:2895–2908

Aspergillus species are ubiquitous molds found in the environment, most abundantly in soil and on decaying vegetation. The genus contains more than 200 species, with more than 30 species now reported to cause infections in humans. *Aspergillus* infection can present with a range of clinical syndromes, from localized colonization of the respiratory tract to devastating invasive disease. This *In Brief* focuses on invasive aspergillosis (IA). Although *Aspergillus* infection in immunocompetent patients is rare, it remains a significant cause of morbidity and mortality in immunocompromised patients. The incidence of IA infections has been increasing, likely related to more aggressive immunosuppressive therapies for certain conditions and increased survival in chronically immunosuppressed patients.

The incidence and severity of IA corresponds directly to a patients' degree of immunosuppression. Patients with prolonged neutropenia are particularly at risk, with reports of an incidence of up to 70% in patients with neutropenia for greater than 30 days. In pediatric populations, the highest rates of IA occur in patients with hematologic malignancy, especially acute myelogenous leukemia. Hematopoietic stem cell transplant patients have 2 peaks of infection: one in the first 40 days after transplant and another 100 days or more after transplant. Later-onset infections are often related to high-dose corticosteroid therapy for graft-versus-host disease. Also, IA is seen in patients with chronic granulomatous disease and other inherited immunodeficiency conditions.

Aspergillus is transmitted through the inhalation of conidia (spores). Studies suggest that most people inhale several hundred *Aspergillus* conidia daily, but infection is avoided through the effective action of pulmonary macrophages and neutrophils. In patients who develop IA there is often a history of a potential exposure in the community, such as gardening or nearby construction. Health-care–associated outbreaks have also been reported and linked to nearby construction, faulty ventilation, or contaminated water sources. Occasionally, cutaneous *Aspergillus* arises in an at-risk patient by direct inoculation at a site of skin injury, such as an intravenous catheter site or under an adhesive dressing (Fig 1). Person-to-person transmission does not occur. The incubation period between exposure and clinical manifestations is unknown but is estimated to be from 2 days to several months depending on species pathogenicity and host factors.

Clinical presentation varies widely and reflects the underlying risk factors of the individual patient. The first presentation may be an unremitting fever in a high-risk patient. Unfortunately, the most immunosuppressed patients have the highest risk of rapid progression but often have minimal symptoms. Invasive disease most commonly involves the respiratory tract due to inhalation of conidia, presenting as pneumonia, tracheobronchitis, or sinusitis. A hallmark of invasive *Aspergillus* disease is the organism's propensity to invade blood vessels, which can lead to thrombosis, dissemination to other organs, and in some cases catastrophic

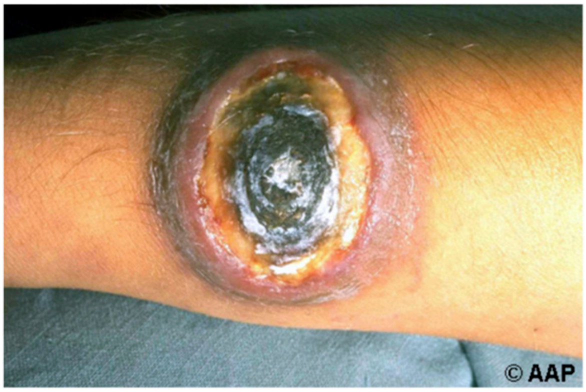

Figure 1. Aspergilloma at the intravenous line site in a 9-year-old boy with acute lymphoblastic leukemia. (Reprinted with permission from Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.)

hemorrhage. Central nervous system disease is the most dreaded of IA syndromes because it is associated with mortality as high as 80% to 90%. Less commonly involved sites of infection include skin, bones, joints, eye/orbit, heart, spleen, kidney, liver, esophagus, and intestine.

Aspergillus infection is notoriously difficult to diagnose. Maintaining a high index of suspicion in high-risk patients is critical. Even in disseminated disease, *Aspergillus* species are usually not recoverable in blood cultures. Tissue biopsy demonstrating hyaline, septate hyphae with acute branching on histologic examination, and growth on fungal culture media are the gold standard of diagnosis. The pathologist may also identify the sporulating conidiophore, whose resemblance to the aspergillum religious device gave rise to the genus name in the 1700s (Fig 2). Obtaining a biopsy is often not feasible due to a high risk of bleeding or secondary infection in patients with AI. Fortunately, adjunctive tests are available to aid in diagnosis. The most frequently used and best studied is a serologic enzyme immunoassay for galactomannan (GM), a component of the cell wall of *Aspergillus*. Results are reported as positive or negative and are not quantitative. A positive test result is suggestive of IA, especially in high-risk patients, but false-positives can occur due to dietary GM (rice, pasta), medications (piperacillin), or other fungi. The GM assay is not reliable in patients with chronic granulomatous disease or Job syndrome. The test has been shown to turn positive approximately a week before radiographic changes or clinical signs develop, leading some centers to prospectively track GM levels in high-risk patients. Other fungal markers, such as 1/3-beta-d-glucan, may be useful for diagnosis, but there are limited data on their accuracy in children and they are less able to differentiate between *Aspergillus* and other fungi. Polymerase chain reaction tests have been developed for serum and bronchoalveolar lavage specimens. Their role in the diagnosis and management of IA is an active area of research.

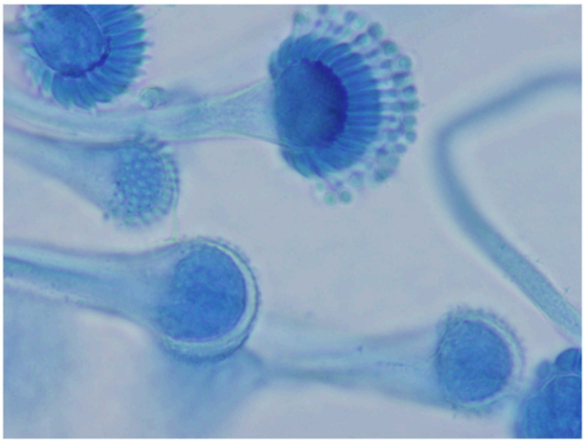

Figure 2. *Aspergillus fumigatus* microscopic image. (Reprinted with permission from Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *AAP Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.)

Due to the rapidly progressive nature of the disease, treatment should not be delayed until definitive diagnosis is made but should begin as soon as IA is suspected.

Voriconazole is the treatment of choice for nearly all forms of IA as outlined in the Infectious Diseases Society of America's 2016 practice guideline. Amphotericin B was historically first-line therapy, but several randomized clinical trials have confirmed voriconazole's superiority. Voriconazole is generally well-tolerated but can interact with immunosuppressive drugs such as tacrolimus and cyclosporine. Treatment duration should be individually tailored for each patient, but generally a minimum of 6 to 12 weeks is required. There are significant differences in metabolism between patients, and serum drug levels should be monitored to ensure safety and efficacy. Other antifungal agents have been studied as alternative options for patients who cannot tolerate voriconazole or for refractory disease, but there is no clear second-line agent of choice. When possible, decreasing the degree of immunosuppression by lowering the dose of immunosuppressive agents or treating prolonged neutropenia with granulocyte colony-stimulating factor or granulocyte infusion is an important adjunct to antifungal therapy. Surgical resection of localized and easily accessible lesions should be considered but in pulmonary disease surgery is reserved for cases where there is significant hemoptysis or lesions are impinging on major airways or vessels.

Prognosis for invasive disease depends on the site of infection, extent of disease, and host factors. Untreated IA has mortality of nearly 100% in most patient groups. An inability to achieve decreased immunosuppression is a significant risk factor for disease progression and death. Although overall survival rates have improved, mortality still exceeds 75% for the highest-risk patients and those with most severe disease. Central nervous system disease outcomes are particularly grave, with rapid progression and greater than 80% mortality.

Due to the high morbidity and mortality associated with IA, there is ongoing effort to find ways to improve outcomes. Early diagnosis and treatment, including periodic monitoring of at-risk patients with GM assays and empirical treatment with voriconazole when IA is suspected, have been shown to improve survival. Prevention efforts for high-risk patients include providing HEPA-filtered, positive-pressure isolation rooms for inpatients and counseling on avoiding gardening or exposure to construction for outpatients. Although there is limited evidence at this time, some have proposed the use of prophylactic antifungal therapy during periods of highest risk. Because patients with IA often have significant underlying comorbidities, treatment of IA should always include consultation with a pediatric infectious disease specialist.

Note. The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US Government.

COMMENT: This *In Brief* reviews a medical entity that primary care pediatricians need to be familiar with in patients they may care for who are immunosuppressed. Because protection against aspergillosis is afforded through neutrophils and alveolar macrophages, patients who do not have these well-functioning protective mechanisms will be at risk. It is important to remember that patients taking corticosteroids may not always present with fever and that aspergillosis may be the first presentation of patients with chronic granulomatous disease. Primary care providers will want to partner with an infectious disease specialist to assist with evaluation and treatment when aspergillosis is a possibility.

– Janet R. Serwint, MD
Associate Editor, *In Brief*

Correction

An error appeared in the print version of the August 2018 review “Group A *Streptococcus*” (Dietrich ML, Steele, RW. *Pediatr Rev*. 2018;39(8):379-391; DOI: 10.1542/pir.2017-0207). In the Summary, the end of the fourth bullet point should read “methicillin-resistant *Staphylococcus aureus*” instead of “methicillin-resistant *Streptococcus aureus*.” The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

ANSWER KEY FOR SEPTEMBER 2018 PEDIATRICS IN REVIEW

Pediatric Cervical Lymphadenopathy: 1. D; 2. D; 3. D; 4. A; 5. E.
Pediatric Solid Tumors in Children and Adolescents: 1. E; 2. E; 3. A; 4. E; 5. E.
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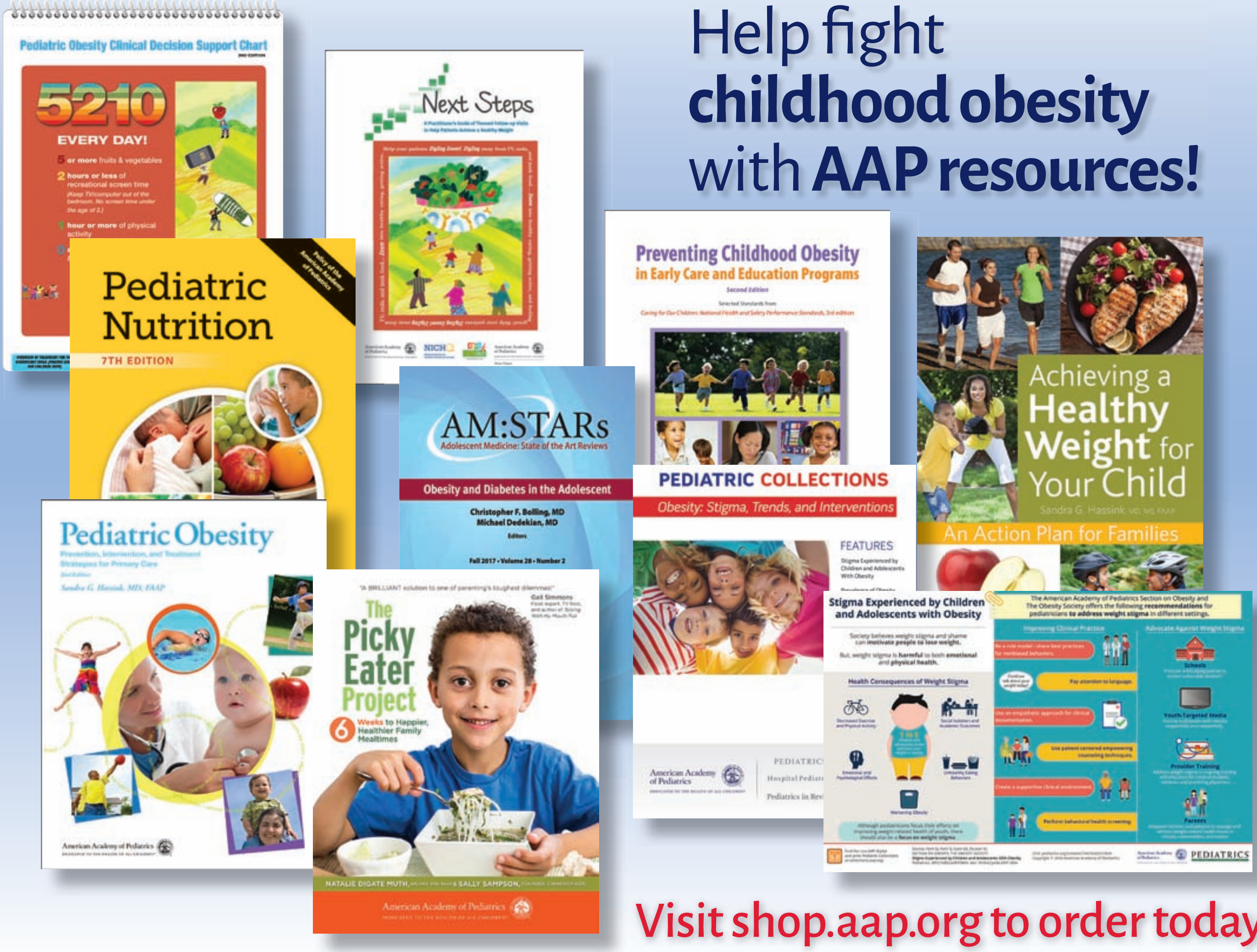
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Visual
Diagnosis

Exophytic Lesions on Tongue and Oral Mucosa

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PRESENTATION

The patient is a 12-year-old girl who presents to her dentist for evaluation of dental abnormalities and to request braces. On examination she is noted to have exophytic lesions on her tongue and oral mucosa. The patient's mother recalls noting "bumps" on the patient's tongue around 5 or 6 years of age, and reports that the lesions have not grown significantly since. The mother also indicates that the patient has always been different in appearance than the younger sister, with full lips, markedly slender and taller body habitus, and splayed toes; she is also excessively flexible in her upper extremities. Review of symptoms reveals alacrima and chronically dry eyes. Her family history is notable only for a paternal grandfather who had colon and thyroid cancer.

On physical examination the patient is well-developed but thin, with a narrow, triangular face, pointed chin, and very full lips. Multiple nodules are noted on the tip of the tongue, buccal mucosa, and maxillary gum line (Figs 1 and 2). Vital signs are normal for age. The heart has a regular rate and rhythm with no murmurs, and the lungs are clear to auscultation. The abdomen is soft, with normal bowel sounds, no masses, and no hepatosplenomegaly. The skin is not distensible, but the patient is able to flex her thumbs to her radii ventrally and extend her fingers dorsally 90°. Her toes are splayed, and the fourth toes are elongated.

Based on the patient's physical appearance with oral nodules suspicious for mucosal neuromas, full lips, marfanoid body habitus, and flexible joints, a concern is raised for a syndromic disorder. Further laboratory evaluation reveals the diagnosis.

DIAGNOSIS

A screening calcitonin level, a serum marker for medullary thyroid carcinoma (MTC), is elevated at 9,601 pg/mL (2,803 pmol/L; laboratory reference values are unavailable for children; 29.4–68.6 pg/mL [8.6–20.0 pmol/L] for females and 20–29 pg/mL [5.8–8.5 pmol/L] for males), leading to the presumptive diagnosis of multiple endocrine neoplasia (MEN) type 2B. Optometric consultation reveals elevations of the bulbar conjunctiva, conjunctival folds, and pronounced corneal nerves. The patient is transferred to a tertiary center for further care.

Evaluation continues with confirmatory laboratory and radiologic studies. Repeated calcitonin level is elevated at 1,359 pg/mL (397 pmol/L; reference range, 0–5.0 pg/mL [0–1.5 pmol/L]). Carcinoembryonic antigen (CEA) level is elevated

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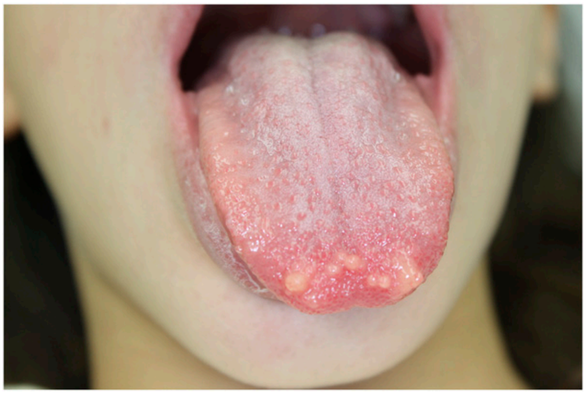

Figure 1. Nodules (neuromas) on the tongue.

at 41.22 ng/mL (41.22 μg/L; reference range, 0–5.0 ng/mL [0–5.0 μg/L]). Plasma metanephrine and normetanephrine levels are normal at 52 pg/mL (263 pmol/L) and 128 pg/mL (699 pmol/L), respectively, making pheochromocytoma unlikely. Complete blood cell count, complete metabolic panel, and urinalysis results are within normal limits. Gene sequencing reveals a heterozygous RET proto-oncogene mutation, pMet918Thr (M918T), commonly associated with MEN2B.

A head and neck computed tomographic (CT) scan reveals a heterogeneous 1.8-cm nodule in the right thyroid, a 0.7-cm mass in the left thyroid, and multiple necrotic levels II, IV, and V cervical lymph nodes. A CT scan of the chest, abdomen, and pelvis is negative for any masses. A nuclear medicine bone scan does not show any evidence of metastatic disease.

DISCUSSION

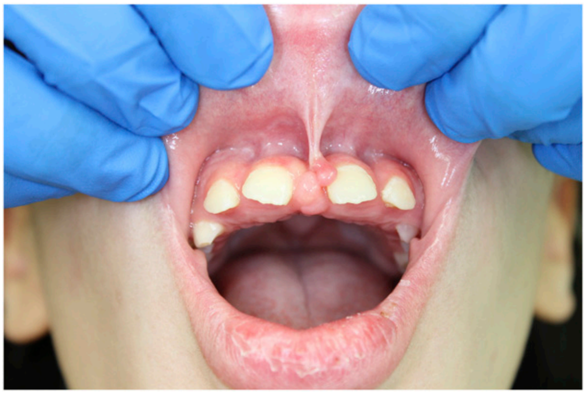

Figure 2. Nodules (neuromas) on the maxillary gum.

Multiple endocrine neoplasia type 2 is a rare autosomal dominant disorder caused by mutations in the RET (**RE**arranged during **T**ransfection) proto-oncogene on chromosome 10. The syndrome involves strong penetrance of MTC, with subtypes differentiated by the presence of other cancers and features. Multiple endocrine neoplasia type 2B is characterized by pheochromocytoma, mucosal neuromas, intestinal ganglioneuromatosis, and a marfanoid body habitus. Of note, hyperparathyroidism is a feature of MEN2A and is not seen in MEN2B. Similar to this patient, 95% of patients with MEN2B will have a mutation of codon 918 in exon 16 of the RET proto-oncogene. Mutations that cause MEN2B develop de novo in 90% of cases. The prevalence of MEN2B is estimated to be 1 in 500,000.

In many cases, the diagnosis of MEN2B is established after the discovery of MTC or pheochromocytoma, as was the case here. However, other overt physical examination findings generally precede tumor presentation, and recognition of marfanoid body habitus, mucosal neuromas, and thickened, protruding lips can lead to earlier diagnosis. Gastrointestinal ganglioneuromas may cause symptoms such as constipation alternating with diarrhea, projectile vomiting, diverticulosis, and megacolon. Diarrhea may be a response to calcitonin or hormones produced locally by ganglioneuromas, which can themselves cause poor peristalsis and contractility. On eye examination, corneal nerve thickening, conjunctival and lid neuromas, perilimbal blood vessel prominence, dry eyes with the inability to cry tears, and increased intraocular pressure are all associated with MEN2B.

Pheochromocytomas occur in 50% of patients with MEN2B, usually during the second to third decades of life, and, in contrast to sporadic pheochromocytomas, are commonly bilateral. These will often present with the classic symptoms of episodic headaches, sweating, and tachycardia, as well as hypertension, palpitations, or tremor. They arise from the adrenal medullas and do not often metastasize. Diagnosis can usually be made on the basis of elevated free plasma or fractionated urinary metanephrine levels, or both, and confirmed by imaging. They can present at younger ages and should be ruled out before thyroid surgery. A recent review of MEN2B cites 12 years old as the youngest reported age for a documented pheochromocytoma in a patient with MEN2B and advises screening beginning at age 11 years in these individuals.

Medullary thyroid carcinoma originates from neural crest–derived parafollicular cells of the thyroid gland. In patients with MEN2B, MTC usually develops in the first decade of life. It is diagnosed after discovery of a thyroid mass or when other clinical features of MEN2B are recognized and screening is performed. Screening for MTC in a patient with suspected MEN2B can be achieved with serum calcitonin, which is the most important diagnostic and prognostic biomarker.

Medullary thyroid carcinoma in MEN2B is a very aggressive tumor, categorized by the American Thyroid Association as the highest risk in the hereditary thyroid cancer group. Metastases are present in 45% of patients with MTC at the time of diagnosis. Preoperative evaluation for metastasis, especially for patients with a calcitonin level greater than 1,000 pg/mL (292 pmol/L), should include whole-body CT, bone MRI, and bone scintigraphy. Initial treatment consists of thyroidectomy with possible lymph node exploration based on burden of disease. After treatment, patients should have ongoing screening of CEA and calcitonin levels every 3 to 12 months, depending on initial and postoperative calcitonin levels, in conjunction with periodic physical examinations and cervical ultrasonography to evaluate for disease progression or relapse.

In the immediate postoperative state, the patient will be at risk for hypocalcemia and should have calcium levels monitored frequently. Thyroidectomy will result in hypothyroidism, and replacement therapy must be initiated.

Prophylactic thyroidectomy is recommended for patients without evidence of MTC given the 100% penetrance of MTC in patients with associated *RET* mutations. In known family members with MEN2B and *Met918T* mutations, thyroidectomy is recommended within the first year of life because local micrometastases of MTC have been found even in children this young.

Persistent or recurrent disease should be treated with careful consideration of potential residual disease, including remaining dissection of compartments with abnormal imaging findings. External beam radiotherapy can be considered in patients with unresectable disease or for adjuvant treatment. The tyrosine kinase inhibitors vandetanib and cabozantinib are also approved for advanced or progressive MTC.

Unfortunately, most patients with de novo MEN2B mutations already have metastatic thyroid cancer by the time they are identified. Studies indicate that the condition is recognized at a mean age of 13 to 16 years, while chances for surgical cure are markedly diminished after age 4 years. In a report including 20 de novo cases, the median delay from presentation with a MEN2B-related complaint to diagnosis was 26 months, ranging from 0 to 18 years. Phenotypic features are less recognizable in infancy, but alacrima is present from birth, and the mean age for development of the mucosal neuromas seems to be 5 to 6 years. In addition, although not present in our patient, 70% of individuals with MEN2B are reported to have gastrointestinal dysmotility, with chronic constipation a common issue beginning in the first months of life. Increasing awareness of these earlier clues might help prompt a closer look for physical signs that would support a diagnosis of MEN2B.

PATIENT COURSE

With no evidence of pheochromocytoma, the patient was cleared for thyroidectomy with bilateral level II to VI neck dissection. The patient tolerated the procedure well and was given levothyroxine, calcium, and vitamin D supplementation after surgery. Postoperative monitoring of serum calcium levels was overall reassuring, necessitating intravenous calcium supplementation only on postoperative day 1. She did not have any evidence of recurrent laryngeal nerve injury but had local incision area numbness.

Pathology confirmed medullary carcinoma in the bilateral lobes and the isthmus, with tumor involvement in the soft tissue margin. Lymph nodes in levels II to IV were positive for metastatic disease in 21 of 62 nodes on the right and in 11 of 48 lymph nodes on the left. There was no evidence of metastasis in 22 nodes submitted from the right neck at level V or in the 1 node submitted from the left neck at that level.

Calcium and vitamin D supplementation were discontinued because the patient's calcium levels remained stable. Levothyroxine dosing was adjusted per guidelines for MTC to maintain thyrotropin within the reference range. The CEA level decreased to 29.28 ng/mL (29.28 μg/L), and the calcitonin level decreased to 774 pg/mL (226 pmol/L) 5 weeks postoperatively, which was indicative of residual disease. The patient is now undergoing evaluation for treatment of residual disease.

Summary

- Medullary thyroid carcinoma has a penetrance of 100% in patients with MEN2B. The tumor is often present from infancy, and sequelae are responsible for major morbidity and mortality when diagnosis is delayed.
- 90% of cases of this familial cancer syndrome are new mutations.
- Recognizing nonthyroid manifestations of MEN2B, such as mucosal neuromas and marfanoid body habitus, or atypical persistent gastrointestinal symptoms or eye complaints, can lead to earlier diagnosis and treatment of medullary thyroid carcinoma, improving patient outcomes.

Note. The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the US Government.

Suggested Readings

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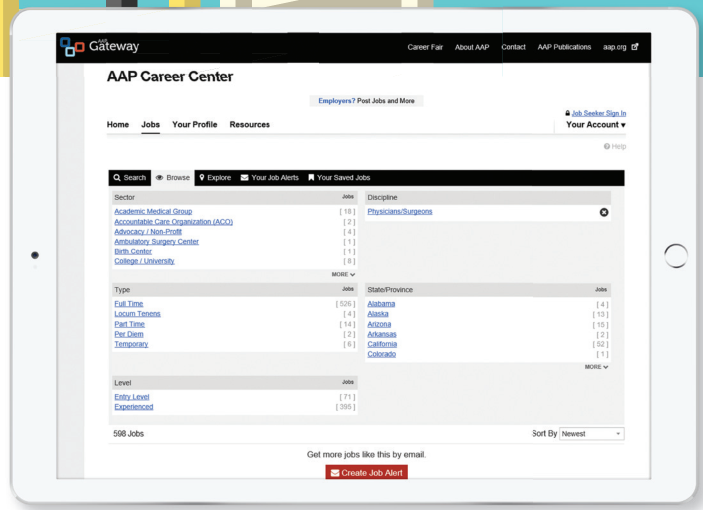

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Overall Approach to Trauma in the Emergency Department

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Practice Gap

Assessing a child who has sustained a multisystem trauma requires a structured assessment of the airway, breathing, and circulation to promptly identify life-threatening injuries and allow for timely lifesaving interventions. This is followed by a more detailed evaluation of the entire body to evaluate for all injuries.

Objectives

After completing this article, readers should be able to:

1. Identify the steps of the primary and secondary surveys used during evaluation of a child who has sustained trauma.
2. Describe the potential life-threatening injuries that may occur after trauma and their treatment.
3. Understand the evaluation and management of a child who has sustained a significant burn.

AUTHOR DISCLOSURE Drs Fein and Fagan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ABCs	Airway, Breathing, and Circulation
ATLS®	Advanced Trauma Life Support®
BSA	body surface area
CSF	cerebrospinal fluid
EMS	emergency medical services
FAST	Focused Assessment with Sonography for Trauma
GCS	Glasgow Coma Scale
MVA	motor vehicle accident
TBI	traumatic brain injury

INTRODUCTION

The importance of trauma in children is readily apparent in that injury is the leading cause of death and disability in children from infancy to young adulthood in the United States. Each year, more than 9,000 children die of serious injury, and approximately 8.7 million children require emergency department care for treatment of their injuries. (1) This surpasses all major diseases in children and young adults. Specifically, motor vehicle accidents (MVAs) are 1 of the top 2 causes of death in children of all age groups. Childhood injuries result in costs exceeding $87 billion annually (1) when accounting for direct medical costs as well as costs to the economy, cost of rehabilitation, and costs to the families of children who survive childhood injury but have resultant lifelong disabilities.

Childhood injury is a public health problem that has multiple facets, ranging from injury prevention to rehabilitation and reintegration into society. The American College of Surgeons created the Advanced Trauma Life Support® (ATLS®) course to help train physicians to face these challenges. Implementation of ATLS pathways to the acute care of injured children has had a major effect on survival. Early recognition and treatment of life-threatening injuries significantly increase the survival rate after major trauma. Definitive diagnosis is not immediately important; rather, having a standardized method for an initial assessment and management of a trauma, such as primary and secondary surveys, is critical.

The approach to evaluation and treatment of trauma in children relies heavily on the trauma team and how well the skills of individuals are integrated into a cohesive functioning unit. The team not only consists of emergency department physicians and nurses but may also include surgeons, anesthesiologists, radiographers, assistants, security, and the blood bank and laboratory staff. The trauma team needs to be well organized and have a leader who designates roles clearly, facilitates clear communication and recognizes the strengths of the individual members of the team, and uses the information that he or she receives from team members. The team leader typically stands at the foot of the bed, facilitating observation of the entire team. Individual members are responsible for the airway and breathing, circulation (including cardiopulmonary resuscitation), intravenous access, performing the primary and secondary surveys, speaking to the family or emergency medical services (EMS) personnel, and keeping a thorough and accurate record of the resuscitation. It is also important that at some point a team member communicates with the primary physician so that he or she is aware of the trauma.

In the United States, trauma centers are verified by the American College of Surgeons from level I (comprehensive service) to level V (limited care). The different levels reflect the types of resources available to the trauma center and the number of patients admitted yearly (2)(3):

- A level I trauma center is a comprehensive tertiary care resource center capable of providing care for every aspect of any injury. Level I pediatric trauma centers must admit 200 or more injured children younger than 15 years of age annually.
- A level II trauma center is able to initiate definitive care for all injured patients. Level II pediatric trauma centers must admit 100 or more injured children younger than 15 years of age annually.
- A level III trauma center can provide prompt assessment, resuscitation, surgery, intensive care, and stabilization of injured patients.
- A level IV trauma center can provide ATLS before the transfer of patients to a higher-level trauma center.
- A level V trauma center provides initial evaluation, stabilization, and diagnostic capabilities and prepares patients for transfer to higher levels of care.

Trauma centers can also be given separate adult and pediatric designations depending on the hospital's facilities, and, thus, it is common for a single facility to have multiple designations (ie, level I adult facility and level II pediatric facility). Center designation is developed at a local or state level and is outlined through legislative and/or regulatory activity. However, one never knows what type of trauma may roll through the emergency department doors, or perhaps even occur inside hospital walls. As such, any medical provider who practices in an emergency department, irrespective of the provider's degree of formal training or the official trauma designation of the hospital, should be familiar with the basic tenets of pediatric trauma care.

Although the basic principles of a trauma evaluation and resuscitation are the same for children and adults—namely, a primary survey to identify immediate life-threatening conditions followed by a more thorough secondary survey—there are specific anatomical, physiological, and emotional differences that must be considered when evaluating a child who has sustained a trauma. These differences and their implications are noted with respect to the primary survey in Table 1.

EVALUATING THE PATIENT WITH CHEST, ABDOMINAL, OR MULTISYSTEM TRAUMA

The Primary Survey

The term "golden hour" refers to the critical period early in the care of trauma patients when management is crucial to optimizing the chances of patient survival. To ensure a standard method of assessment, the initial evaluation of a child who has sustained significant trauma has been laid out by the American College of Surgeons in ATLS: a primary survey and resuscitation, followed by a secondary survey. (4) The primary survey is completed rapidly and systematically, with the goal of identifying life-threatening conditions and treating them. Patency of the airway, adequate respiratory effort, circulatory support, and neurologic status are evaluated. During the course of resuscitation, the primary survey is repeatedly reassessed to identify any changes and potential deterioration. Table 2 summarizes the steps of the primary survey and the life-threatening conditions that can be identified at each step. It is crucial to attend to the critical aspects in each step of the primary survey before moving on to the next. Typically, enough information is obtained during the primary survey for the physician to determine whether transfer to a higher-level facility is necessary. Providers should wear personal protective equipment as necessary before initiation of the evaluation and resuscitation of the trauma victim.

TABLE 1. **Anatomical and Physiological Differences Between Children and Adults**

SYSTEM	DIFFERENCE FROM ADULTS	IMPLICATION
Airway	Airway is shorter and narrower Larynx and vocal cords in infants are more anterior Tongue is relatively larger in the oropharynx Epiglottis is long and floppy Narrowest point of the airway is below the cricoid cartilage	Differences in the oropharyngeal anatomy can make intubation more difficult, require different-sized endotracheal tubes (including potential use of uncuffed endotracheal tubes), require a different laryngoscope
Breathing	Infants are obligate nasal breathers	Nasal obstruction can impede respiratory effort
	The chest wall is more compliant	Rib fractures and external signs of trauma may not be present with significant intrathoracic injuries
Circulation	Circulating blood volume is increased (∼70–80 mL/kg)	Children remain normotensive for a longer time despite significant blood loss
Disability	Larger occiputs causing passive flexion of the cervical spine The fulcrum of the spine is higher (located at C2-C3) Less-developed cervical musculature Vertebral bodies have facet joints that are horizontally oriented and anteriorly wedged	Anatomical differences result in different types of head and cervical spine injuries than in adults, even with similar forces
	Cervical segments are hypermobile during flexion	Greater potential for spinal cord injury without radiographic abnormality
	Fontanelles present in infants	More subtle signs of increased intracranial pressure may develop before herniation
Exposure	Proportionally larger body surface area	Hypothermia develops more rapidly
	Smaller body mass	Energy imparted results in a greater force applied per body surface area
	Close proximity of multiple organs	Higher frequency of multiple injuries
Emotional	Long-term emotional sequelae may include personality changes and cognitive handicaps	May be necessary to involve mental health professionals in both the acute care and the rehabilitation of the injured child

Airway Maintenance with Cervical Spine Protection

Airway assessment consists of evaluation of the patency of the airway and the ability of air to pass freely into the lungs. A child who is speaking clearly has an unobstructed airway. Airway evaluation includes inspection for foreign bodies and any facial or tracheal/laryngeal fractures that may potentially compromise the airway. Suctioning the oropharynx may be necessary for a complete evaluation. Signs of upper airway obstruction include stridor, hoarseness, subcutaneous emphysema of the neck, use of accessory muscles, and facial or oropharyngeal burns (see the Burns section later herein). Securing an airway may be accomplished via endotracheal intubation. If endotracheal intubation is unsuccessful, a surgical airway, such as a surgical or needle cricothyroidotomy, should be performed.

While managing the airway, it is crucial to maintain the cervical spine in a neutral position. Although a cervical collar facilitates immobilization, if it must be temporarily removed, a trauma team member must manually stabilize the cervical spine. The chin-lift maneuver, where the mandible is gently lifted from the submental area, or the jaw-thrust maneuver, where the angles of the mandible are manually displaced forward, should be used in place of the head-tilt maneuver, which can exacerbate a cervical spine injury. Children with midline cervical spine tenderness, those who have altered mental status, or those who have sustained severe multisystem trauma require a radiographic evaluation of the cervical spine, which can be obtained after the patient has been stabilized.

Breathing

After ensuring a secure airway, the next step is evaluation of the patient's breathing, specifically, ensuring that adequate oxygenation and ventilation are maintained. The patient's breathing should be observed to ensure appropriate and symmetrical chest rise. The chest wall should be auscultated, palpated, and, if ambient decibel level allows, percussed to evaluate for any abnormalities. Signs of respiratory distress include accessory muscle use, grunting, bradypnea or tachypnea, decreased chest wall movement, shallow respirations, and cyanosis. High-concentration oxygen should be applied, and the patient should be monitored using a pulse oximeter and a capnometer. Respirations can be assisted with bag-mask ventilation before intubation if the respiratory effort is not sufficient. A portable chest radiograph can be obtained and may provide significant information.

TABLE 2. **Life-threatening Injuries that May Be Identified on the Primary Survey**

SYSTEM	LIFE-THREATENING INJURY	TREATMENT
Airway	Airway obstruction	Endotracheal intubation if possible; if not, needle cricothyroidotomy with jet insufflation or surgical cricothyroidotomy
Breathing	Tension pneumothorax	Needle decompression in second intercostal space
	Open pneumothorax	Application of occlusive dressing that is secured on 3 sides
	Massive hemothorax	Placement of chest tube and hemodynamic support
	Flail chest	Respiratory support, fluid resuscitation, and analgesia
	Pulmonary contusion	Respiratory support
Circulation	Cardiac tamponade	Pericardiocentesis

During the course of the assessment of breathing, several life-threatening conditions that may impair ventilation and require immediate intervention may be identified, as follows (5):

- A tension pneumothorax results when air is trapped in the intrathoracic space without a way to escape. There is resultant ipsilateral lung collapse and subsequent mediastinal and tracheal shift away from the tension pneumothorax. There will be respiratory distress, tachycardia (and eventually hypotension), ipsilateral absence of breath sounds, and possible jugular venous distention (which may be difficult to ascertain on an infant or young child). A tension pneumothorax is a clinical diagnosis and is treated with needle decompression by inserting a needle into the second intercostal space in the midaxillary line. A chest tube will need to be placed after this temporizing measure is completed.
- An open pneumothorax occurs when there is direct communication between the intrathoracic cavity and the external environment (typically due to penetrating trauma) that results in an influx of air through the wound into the intrathoracic cavity with every inspiration. An open pneumothorax is treated by applying an occlusive dressing that is taped on 3 sides, thereby allowing air to leave the chest with expiration but preventing it from entering on inspiration.
- A massive hemothorax occurs when blood accumulates in the intrathoracic cavity, resulting in tachycardia, hypotension, ipsilateral decreased breath sounds, and dullness to percussion. A massive hemothorax requires placement of a chest tube and volume resuscitation.
- Flail chest occurs when trauma results in several contiguous ribs fractured in more than one place. The resultant segment moves paradoxically with respiration, preventing adequate ventilation. Flail chest may be a clinical diagnosis or may be found on chest radiography. It is treated with adequate respiratory support, fluid resuscitation, and analgesia. Flail chest is associated with pulmonary contusions—injury to the underlying lung—that can result in hypoxia and respiratory compromise.

Circulation

After ensuring that there are no immediate life-threatening conditions associated with breathing, the evaluation moves forward to the assessment of the patient's circulatory status. This is accomplished by evaluating the patient's level of consciousness, the presence and quality of pulses, skin color, and blood pressure and identifying any sources of external hemorrhage. Direct pressure is applied to any visibly hemorrhaging area, 2 large-bore intravenous lines are placed (or an intraosseous line if vascular access is difficult to obtain), laboratory work (including type and cross) is obtained, and warm crystalloid fluid resuscitation is initiated, in addition to blood transfusions if necessary. Additional sources of internal hemorrhage should be considered (chest, abdomen, pelvis, and long bones). A normal blood pressure should not be considered reassuring because hypotension secondary to bleeding is a late sign of shock in children and is suggestive of massive blood loss. Children with abdominal trauma presenting in shock should promptly be taken to the operating room to identify the source of hemorrhage.

In addition to a massive hemothorax, the immediate life-threatening condition that may be identified during evaluation of the circulation is cardiac tamponade. Tamponade occurs when blood accumulates rapidly inside the pericardium, restricting normal cardiac activity. Symptoms of tamponade include hypotension, jugular venous distention, and muffled heart sounds, together known as the Beck triad, and presence of a pericardial effusion on ultrasonography (see the secondary survey). A pericardiocentesis can be performed to remove blood; however, surgery will ultimately be required to find and repair any cardiac injury. (5)

Disability

After evaluation of the airway, breathing, and circulation (ABCs), the next step is performing a brief neurologic assessment. This can be accomplished using the Glasgow Coma Scale (GCS) (Table 3), checking the pupils, and, if possible, assessing for any localizing neurologic findings. See the Head Trauma section later herein for further details.

Exposure

It is important to completely undress the patient to allow for a thorough secondary survey; however, preventing hypothermia is crucial. Warmed intravenous fluids should be used, and the ambient temperature in the trauma bay should ensure that the patient stays warm.

A gastric tube should be placed to help decompress the stomach, reduce aspiration risk, and assess for gastrointestinal hemorrhage, and a urinary catheter should be placed to carefully monitor urinary output. Midface trauma and/or suspicion of a cribriform plate fracture are contraindications to placement of a nasogastric tube. Concern for a urethral injury, including visualization of blood at the urethral meatus, ecchymosis in the perineum, or palpation of a high-riding prostate, should prompt a retrograde urethrogram before urinary catheter insertion.

TABLE 3. **Adult and Pediatric Glasgow Coma Scales**

		ADULT	PEDIATRIC
Eye opening	4	Spontaneously	Spontaneously
	3	To speech	To voice
	2	To pain	To pain
	1	No response	No response
Verbal response	5	Oriented	Coos, babbles, interacts
	4	Confused	Irritable, crying
	3	Inappropriate words	Cries to pain
	2	Incomprehensible sounds	Moans
	1	No response	No response
Motor response	6	Follows commands	Spontaneous movement
	5	Localizes pain	Withdraws to touch
	4	Withdraws from pain	Withdraws from pain
	3	Decorticate posturing	Decorticate posturing
	2	Decerebrate posturing	Decerebrate posturing
	1	No response	No response

The Secondary Survey

Once the primary survey has been completed, resuscitation of the injured child has commenced, immediate life-threatening injuries have been treated, and the patient has been stabilized, the secondary survey proceeds. The secondary survey consists of a complete history and physical examination and searching for any injury that may have occurred, no matter how small. The patient's age or clinical condition may preclude them from relaying details of the trauma, so information should be sought from a family member, other witnesses of the trauma, and EMS workers. Important information to obtain about the patient and the clinical scenario can be captured by the mnemonic AMPLE:

- Allergies the patient has
- Medications the patient is on
- Past medical history
- Last time the patient ate
- Events related to the sustained trauma (and any intervention by EMS)

As detailed a mechanism of injury as possible should be sought because important information can be gleaned from even a seemingly trivial statement. If the size of the trauma team allows, an individual can be assigned to speak with the family and/or EMS to obtain information. One should always consider underlying anatomical or pathophysiological processes (eg, Wilms tumor) and nonaccidental trauma if the degree of physical findings is out of proportion to the proposed mechanism.

The complete physical examination involves a head to toe evaluation for any injury, no matter how small, including (but is not limited to) the following (4):

- Evaluation of the head and face for scalp lacerations, suspected skull fractures, signs of ocular trauma, maxillofacial and dental trauma, and reassessment of neurologic status
- Evaluation of the neck for signs of blunt or penetrating trauma and vascular injury
- Evaluation of the cervical spine for signs of injury. Although cervical spine stabilization is part of the primary survey, during the secondary survey further evaluation of the cervical spine is warranted, including radiographic evaluation of the cervical spine if the stability and integrity of the cervical spine cannot be ensured on the clinical examination
- Inspection and palpation of the chest for signs of blunt or penetrating trauma, obtaining a chest radiograph if clinically indicated and not previously obtained

- Inspection and palpation of the abdomen for signs of blunt or penetrating trauma, auscultation of bowel sounds, consideration of a pelvic radiograph to evaluate for a pelvic fracture, and performance of a Focused Assessment with Sonography for Trauma (FAST) examination
- Evaluation of the genital area for signs of trauma, rectal examination (if clinically indicated), evaluation for blood at the urethral meatus
- Inspection and palpation of extremities for signs of blunt or penetrating injury, obtaining imaging of areas of concern, and splinting injuries as clinically indicated. Care should be taken to roll the patient to the side while maintaining cervical spine stabilization so that the back, buttocks, and thoracic and lumbar spine can also be evaluated for signs of trauma
- Evaluation for signs of peripheral neurologic injury as allowed by the clinical condition

Potential life-threatening injuries that can be found during the secondary survey include simple pneumothorax, hemothorax, aortic disruption, tracheobronchial injury, diaphragmatic injury, and esophageal rupture.

The FAST examination is a point-of-care sonographic assessment looking for signs of intra-abdominal and intrathoracic injury. The FAST examination is an invaluable adjunctive tool to the secondary survey as it is performed at the same time as other resuscitative efforts by another member of the trauma team and there is no delay in receiving imaging results because they are interpreted bedside by the trauma team. Sonographic views of the FAST examination include a subxiphoid view of the heart (evaluating for a pericardial effusion), evaluation for blood in the Morison pouch (the potential space between the liver and the kidney), the perisplenic recess, and the retrovesicular area in males and the Douglas pouch (the potential space between the uterus and the rectum) in females. Other adjunctive tools include laboratory work, radiographs, computed tomographic (CT) scans, and an electrocardiogram.

Performance of the secondary survey is crucial to ensuring a comprehensive evaluation of the patient who potentially sustained multisystem trauma. Frequent reassessments of both the primary and secondary surveys are crucial to identify subtle signs of decompensation and ensure that early and appropriate interventions can be undertaken to restabilize the child if necessary.

HEAD AND CENTRAL NERVOUS SYSTEM TRAUMA

Traumatic brain injury (TBI) is a leading cause of death and disability in children in the United States. Children can sustain head and/or central nervous system injury as either part of a multisystem trauma (eg, during an MVA) or as an isolated injury (eg, struck by an object). In addition, nonaccidental trauma must always be considered, especially when there is head trauma in a nonambulatory child or if the story does not make sense given the developmental stage of the child. Younger children are at a higher risk for sustaining head trauma because their heads are proportionally larger than the rest of their bodies and their skull is less protective than that of an adult. In addition, differences in the ratio of the brain to intracranial spaces result in less cushioning of the brain in cerebrospinal fluid (CSF) and, thus, less protection when an accident happens.

Brain injury secondary to trauma can be due to direct trauma between the brain and the internal aspect of the skull (cerebral contusion), shearing forces (diffuse axonal injury), or secondary to intracranial bleeding leading to a sudden increase in intracranial pressure (epidural or subdural hematomas). The Monro-Kellie doctrine states that the total volume of intracranial contents, which normally consists of brain, CSF, and arterial and venous blood, must remain stable because the skull is a nonexpandable container. Injuries causing an epidural or subdural hematoma will ultimately result in increased intracranial pressure once the CSF and intravascular blood has been displaced from the intracranial space by the expanding hematoma. An older child with a subdural or epidural hematoma will present with headaches, vomiting, and altered mental status, whereas an infant may initially present with only a bulging fontanel before more overt signs of an acute increase in intracranial pressure from an intracranial bleed. The Cushing triad (bradycardia, hypertension, and respiratory depression) signifies increased intracranial pressure and impending herniation. On the other hand, hypotension in the setting of head trauma should prompt evaluation for a source of extracranial blood loss.

Evaluation of a child who sustained head trauma, whether in conjunction with multisystem trauma or in isolation, begins with the organized process of the primary survey (the ABCs) as detailed previously herein. Special consideration should be given to the Disability section of the primary survey. Two commonly used assessments of disability include the AVPU scale and the GCS. The AVPU scale assesses whether a child is Awake and whether he or she responds to Verbal stimuli, responds to Pain, or is Unresponsive. The GCS measures 3 components, verbal, motor, and eye responses, and has been slightly modified for pediatrics (Table 3). A GCS score of 13 or greater is usually indicative of a minor TBI, a score of 9 to 12 is considered a moderate TBI, and a score of 8 or less is typically indicative of a severe TBI. Children with a GCS score of 8 or less should be intubated to protect their airway and should undergo head CT and a neurosurgical consultation. A child with a GCS score of 9 to 12 should also undergo head CT and be admitted for neurologic monitoring. Children with a GCS score of 13 or greater may or may not require head imaging. Pupillary examination is also a key aspect of the evaluation of a child's disability. For instance, asymmetrical pupils may be a sign of impending herniation after trauma, and pinpoint pupils may represent an opiate overdose as the cause of decreased responsiveness.

Multiple studies have sought to identify cohorts of children who are at low risk for having sustained a clinically important TBI and, thus, can possibly forego a head CT scan and being exposed to the risks of radiation. These include (but are not limited to) the PECARN (Pediatric Emergency Care Applied Research Network), (6) CATCH (Canadian Assessment of Tomography for Childhood Head injury), (7) and CHALICE (Children's Head injury ALgorithm for the prediction of Important Clinical Events) (8) rules. All of these clinical decision rules use different risk factors to identify low-risk children (Table 4); however, they are all very sensitive, with extremely high negative predictive values. (9) Currently, 1 or more of these rules are typically used when clinicians are faced with a child who sustained head trauma and looks very well on examination.

A concussion is a type of TBI that results from a blow to the head or elsewhere to the body (with force transmitted to the head) that may or may not be followed by loss of consciousness. A concussion can present with a panoply of symptoms, including any of the following: headache, amnesia, dizziness, vomiting, fatigue, vision problems, sensitivity to light or noise, imbalance or gait problems, difficulty concentrating, and emotional lability.

There are standardized assessment tools developed to diagnose concussions to ensure that children are not placed back into a situation that could risk further injury. Although there are varying opinions about what should constitute "cognitive rest" with respect to concussion management, it is widely believed that there should be a period of "physical rest" and a progression of return to play that commences when all concussive symptoms have resolved. The Centers for Disease Control and Prevention has an informative website that provides information to parents, coaches, schools, and practitioners (http://www.cdc.gov/HeadsUp).

Spinal cord injury is comparatively infrequent in children. Injuries to the spinal cord result in a presentation that depends on the exact spinal level (ie, C7 vs L1) and cord location (ie, anterior cord, hemisection of cord) of the injury. The immature spine is significantly more flexible due to a relative laxity of the interspinous ligaments, flat facet joints, and vertebrae that are wedged anteriorly. This flexibility can result in an injury called SCIWORA—Spinal Cord Injury WithOut Radiographic Abnormality—that typically occurs in the cervical region. Recognition of this entity is important because a significant number of spinal cord injuries can have normal cervical spine radiographs. Thus, if a spinal cord injury is suspected based on history or physical examination findings and there are normal cervical spine radiographs, magnetic resonance imaging of the spine should be performed.

BURNS

Burns represent a unique aspect in pediatric trauma. They can occur in conjunction with a larger multisystem trauma (eg, MVA with subsequent fire), which can complicate the resuscitation and lead to higher morbidity; however, they typically occur in isolation as an accidental burn (eg, splash or spill of hot water). It is important to always consider an inflicted burn as due to possible child abuse. Inflicted burns may be patterned, have sharp demarcations including being perfectly circular, spare intertriginous areas, or not be consistent with the mechanism provided.

Assessment of a burn includes determination of the amount of skin involved (body surface area [BSA]) and the depth of the burn. This is typically accomplished using the "rule of nines," which divides the body of an adult or older child into multiples of 9%. The trunk and back are 18% each, the anterior and posterior lower extremities are 9% each, the anterior and posterior upper extremities and head are 4.5% each, and the genital area is 1%. This is slightly modified for infants to account for the comparatively large head. Alternatively, the patient's hand (including fingers) represents approximately 1% BSA.

Burns can be characterized into 3 different depths as follows:

- Superficial burns—red, painful, and do not blister (eg, most sunburns)
- Partial-thickness burns—typically red and swollen, exquisitely painful, appear wet, and are characterized by blistering
- Full-thickness burns—waxy or leathery appearance, are not painful to the touch, and the skin tends to feel dry

Superficial burns are not included when calculating the BSA involved. Recognition that blistering may take time to develop is important because areas initially characterized as a superficial burn may truly be a partial-thickness burn only to develop the blistering several hours later.

TABLE 4. **Comparison of Risk Factors Potentially Necessitating a Head Computed Tomographic Scan in Children after Head Trauma**

RISK FACTOR	CATCH	CHALICE	PECARN
GCS score	<15 (>2 h after injury)	<14 (<15 if <1 y)	<15
Suspected fracture	Yes (suspected open or depressed fracture)	Yes (suspected depressed or penetrating fracture)	Yes (palpable skull fracture [only if <2 y])
Sign of basilar skull fracture	Yes	Yes	Yes (only if >2 y)
Change in mentation	Yes (irritability on examination)	Yes (abnormal drowsiness)	Yes (including not acting normally as per parent if <2 y)
Loss of consciousness	No	Yes (>5 min)	Yes if >5 sec if <2 y, yes if >2 y
Headache	Yes (if worsening)	No	Yes (if severe and >2 y)
Hematoma	Yes (large, boggy)	Yes (any bruise or swelling)	Yes (if nonfrontal and <2 y)
Vomiting	No	Yes (≥3 episodes)	Yes (if >2 y)
Amnesia	No	Yes	No
Concern for nonaccidental trauma	No	Yes	No
Seizure	No	Yes (if no history of epilepsy)	No
Focal neurologic findings	No	Yes	No
Dangerous mechanism of injury	Yes (MVC, fall ≥3 ft or 5 stairs, fall off bicycle without helmet)	Yes (high-speed MVC [>40 mph] as occupant or pedestrian, fall >3 ft, high-speed projectile injury)	Yes (MVC with ejection, death, or rollover; pedestrian or cyclist struck by car; fall >3 ft [<2 y] or >5ft [>2 y]; high-speed projectile injury)

CATCH=Canadian Assessment of Tomography for Childhood Head injury, CHALICE= Children's Head injury ALgorithm for the prediction of Important Clinical Events, GCS=Glasgow Coma Scale, MVC=motor vehicle crash, PECARN=Pediatric Emergency Care Applied Research Network.

Fluid management is crucial in children who have sustained significant burns. In addition to providing maintenance fluid, ongoing fluid losses must be accounted for with fluid resuscitation. One of the commonly used calculations to determine the fluid requirements for the first 24 hours after a significant burn is the Parkland formula: 4 mL/kg × total BSA affected. Half of this fluid is administered in the first 8 hours, the remaining half over the next 16 hours. Maintenance fluid is typically administered as well in younger children. Recently a nomogram has been created to assist in rapid calculation of appropriate volume administration. (10)(11) Other principles of burn management include analgesia, debridement, dressings, and tetanus vaccination.

Other issues to consider when evaluating a patient who has been burned include the possibility of an inhalational burn, as well as exposure to other inhalants from a fire. Signs of an inhalational burn include singed nose hairs, carbonaceous sputum, hoarseness, stridor, drooling, and oropharyngeal edema. Children with facial burns should be monitored closely for progression of an inhalational injury, as the initial symptoms may be subtle. Airway management of a patient who has sustained an inhalational injury can be very difficult and should be handled by a trained specialist. Children who have been in a residential or industrial fire are at risk for both carbon monoxide and cyanide poisoning because these are common byproducts of decomposition of both synthetic and natural substances.

Although many burns can be managed at any medical locale, certain thermal burns are recommended to be treated at a burn center, including (but are not limited to) any full-thickness burn; partial-thickness burns larger than 10% BSA; burns including genitalia, face, hands, feet, or major joints; inhalational injuries; and children in centers without the necessary qualified personnel or equipment. (12)

ORTHOPEDIC TRAUMA

Orthopedic trauma is the most common form of trauma in children and occurs both in the setting of multisystem trauma and, more commonly, in isolation. When evaluating a child who has sustained multisystem trauma, orthopedic considerations include cervical spine stabilization (see previously herein) and evaluation for a pelvic fracture, which, similar to a femur fracture, can lead to significant hemorrhage that may not be easily appreciated on the physical examination. Areas identified during the secondary survey as a concern for fracture or dislocation should be appropriately imaged.

Open fractures, where there is direct communication between the fracture and the external environment, are an orthopedic emergency. An open fracture may be extremely obvious, with bone protruding from the skin, or it may be as subtle as a small break in the skin, which in actuality represents penetration of a fractured bone through the epidermis that has since receded back underneath the skin. In the latter case, excessive bleeding, crepitus, and blood with visible fat globules at the wound site may be indications that the small wound is actually an open fracture. Open fractures require orthopedic consultation, removal of debris and cleaning of any protruding bone with saline, reduction of the fracture, administration of tetanus immunoglobulin and tetanus toxoid as necessary, and prophylactic antibiotic drug therapy.

In addition to open fractures, fractures that result in neurovascular compromise are also orthopedic emergencies. Neurovascular compromise can result from a direct nerve or vascular injury from a displaced fracture or can occur hours or days later due to compartment syndrome. Assessment of motor function, sensation, pulse quality, and capillary refill of an injured extremity are critical parts of the physical examination. Any apparent neurovascular dysfunction should be noted, and if occurring in close proximity to the trauma may necessitate urgent manipulation and reduction.

Compartment syndrome occurs due to increased pressure in a fascial compartment that exceeds venous pressure, compromises circulation, and results in ischemia of nerve and muscle, causing tissue damage. The diagnosis of compartment syndrome should be suspected in a patient who has pain out of proportion to the underlying injury and/or pain on passive stretching of muscles of an affected extremity. Other signs and symptoms, such as paresthesia, paralysis of an extremity, pulselessness, pallor, and poikilothermia, the so-called 5 *P*s of compartment syndrome, are late findings. Compartment syndrome is a true surgical emergency and requires emergent orthopedic consultation and a decompressive fasciotomy.

Summary

- Trauma remains a major cause of morbidity and mortality in children.
- On the basis of some research evidence and consensus, the appropriate method of evaluating a child who has sustained multisystem trauma is using an organized, systematic approach with primary and secondary surveys with the goals of resuscitation, stabilization, and identification and treatment of life-threatening injuries. (4)(5)
- Both multisystem trauma and other forms of seemingly isolated trauma, including head trauma, burns, and orthopedic trauma, should always be carefully evaluated to ensure complete assessment of all injuries, no matter how small. The possibility of nonaccidental trauma should remain on the differential diagnosis of an injured child.
- Based on strong research evidence, it is possible to identify a cohort of children who have sustained head trauma who are at low risk for a significant intracranial injury and can likely forego a computed tomographic scan of the head. (6)(7)(8)
- Fluid management is crucial for children who have sustained significant burns. The Parkland formula can be used to calculate the fluid requirement in conjunction with maintenance fluids.
- It is crucial to ensure communication with the patient's primary physician, whether the child sustained severe multisystem trauma or a simple fracture, because he or she will play a leading role in the ongoing rehabilitation processes and reintroduction of the child back to normal activity.

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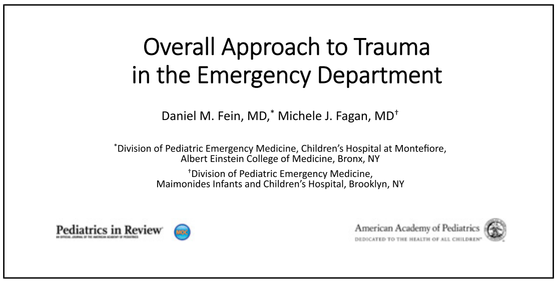

Overall Approach to Trauma
in the Emergency Department

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1. A pediatric tertiary care hospital has a trauma service with the following characteristics:

   Comprehensive tertiary care resource center
   Can provide care for every aspect of any injury
   Admits 125 children younger than 15 years of age annually for trauma-related injuries

   According to the American College of Surgeons trauma classification system, which of the following represents the trauma service level that is offered by this hospital?

   A. Level I.
   B. Level II.
   C. Level III.
   D. Level IV.
   E. Level V.

2. A 3-year-old child is brought to the emergency department after a high-speed motor vehicle collision. This hospital has a level III pediatric trauma center. The child was properly restrained in the back seat of the car. The car flipped several times before coming to rest on its side. The child has been transported with a cervical collar in place. He has an initial Glasgow Coma Scale score of 8. He has a large hematoma to the forehead, as well as a 4-cm laceration to the left parietal scalp that is oozing blood. His heart rate is 160 beats/min, respiratory rate is 12 breaths/min, blood pressure is 82/55 mm Hg, and pulse oximetry is 91% on room air. He is moving all of his extremities spontaneously. Which of the following issues must be addressed immediately during the primary survey?

   A. Arrange for transfer of the patient to a level I trauma center.
   B. Consult neurosurgery due to the depressed level of consciousness.
   C. Insert an endotracheal tube to protect the airway and assist with breathing.
   D. Order neck radiographs to assess for cervical spine injury.
   E. Repair the laceration to prevent further bleeding.

3. A 12-year-old child sustained a nondisplaced pelvic fracture after a motor vehicle collision and is brought to the emergency department by emergency medical services. After performing the primary survey, the emergency department team is preparing to insert a urinary catheter. The presence of which of the following clinical findings warrants performing a retrograde urethrogram before insertion of the urinary catheter in this patient?

   A. Blood visualized at the urethral meatus.
   B. Liver laceration has also been identified.
   C. The patient has diffuse abdominal pain.
   D. There is a large laceration at the iliac crest.
   E. Urinary catheter placement should be ordered in any obtunded trauma victim.

4. A 6-year-old girl sustained a massive head trauma after a head-on collision between 2 motor vehicles. The patient was an unrestrained passenger. She has a Glasgow Coma Scale score of 3. An endotracheal tube was placed at the scene by the transporting helicopter crew. Her blood pressure on arrival at the emergency department is 140/90 mm Hg, heart rate is 60 beats/min, and pulse oximeter reading on 50% oxygen is 98%. She has a large hematoma involving most of the right parietal region. A computed tomographic scan of the brain is performed, neurosurgery is consulted, and the patient is started on mannitol per the Monro-Kellie doctrine. Which of the following principles is the basis for the Monro-Kellie doctrine?

   A. Arterial blood is at higher pressure than venous blood.
   B. Blood is denser than water.
   C. Hyperventilation causes cerebral vasoconstriction.

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D. Systemic blood pressure must always exceed intracranial pressure.
E. The skull is a nonexpandable container.

5. A 14-year-old boy is brought to the emergency department after sustaining a closed head trauma. The patient was playing soccer at school when he ran into his teammate and his head hit the teammate's shoulder bone. He felt dizzy immediately but had no complaints 5 to 10 minutes after the incident. There is no loss of consciousness, no vomiting, no headaches, and no vision changes. On examination in the emergency department, he is oriented to time, place, and person. There is a small bump over the left parietal area of the skull with no open wounds or hematomas and no depressed skull ridge on palpation. The remainder of his physical examination, including his neurologic examination, is within normal limits. In this patient with traumatic brain injury, which of the following management decisions is based on the primary purpose of the PECARN (Pediatric Emergency Care Applied Research Network), CATCH (Canadian Assessment of Tomography for Childhood Head injury), and CHALICE (Children's Head injury ALgorithm for the prediction of Important Clinical Events) rules?

A. Assess whether the patient is at risk for posttraumatic learning problems requiring special accommodations at school.
B. Determine the need for neurosurgical follow-up.
C. Determine when the patient can return to playing sports.
D. Forego a computed tomographic scan of the brain.
E. Predict the need for formal psychological testing.

Human and Animal Bites

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Practice Gaps

1. To provide appropriate care to children who have sustained human or animal bites, health practitioners should be able to manage bite wounds to minimize the risk of the child developing serious or even fatal infections.
2. Clinicians should be able to implement strategies for providing anticipatory guidance regarding pet ownership and animal contact outside the household as part of the health supervision visit.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology of human and animal bites in children.
2. Identify common etiologic pathogens associated with human and animal bite wound infections.
3. Apply strategies oriented to prevent the development of bite wound infections and to decrease the risk of fatal infections such as rabies or tetanus.
4. Manage bite wounds adequately to decrease morbidity and mortality associated with these.
5. Develop strategies for providing education and anticipatory guidance to children and their caregivers regarding safety with pets and animal contact.

Abstract

In the United States, nearly 56% of households owned a pet in 2011 according to the *2012 U.S. Pet Ownership & Demographics Sourcebook* by the American Veterinary Medical Association. The survey also reports that approximately 70 million dogs and 74 million cats lived in households in the United States during the same year. (1)

Human and animal bites are a frequent cause of primary care and emergency department visits for children. It is estimated that 250,000 human bites, 400,000 cat bites, and 4.5 million dog bites occur in the United States each year in both adults and children. (2) In the United

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ABBREVIATIONS

AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
MRSA	methicillin-resistant *Staphylococcus aureus*
spp.	species

States, approximately 10% of all human bites will become infected in a child with a bite wound. The infection rate of dog bites in children is 20%. Cat bite infection rates in children vary but can be up to 50%. Each type of bite wound has a predisposition for sex and/or age. Infected bite wounds manifest with swelling, erythema, and tenderness with or without drainage of the affected site and can lead to serious complications. Most animal bite wounds are polymicrobial in nature. *Pasteurella* species (spp.) is the most common organism isolated from both cat and dog bites. The microbiology of human bites consists of both aerobic and anaerobic bacteria.

Basic medical management of bite wounds includes thorough cleansing and debridement. Irrigation, closure, and need to obtain culture depend on the type of bite wound, the appearance of the wound, the and timing of medical evaluation after the initial injury. Amoxicillin-clavulanate is the antibiotic of choice for prophylaxis and empirical therapy for children who are not allergic to penicillin. With most animal bites being preventable injuries, healthcare providers caring for children have an important role discussing pet safety with the child and the family.

INTRODUCTION

Human and animal bites are a frequent cause of primary care and emergency department visits for children. Historically, the morbidity of such injuries was quite significant, with 1 study reporting one-third of patients requiring amputation if care was sought more than 24 hours after initial injury. However, the morbidity has greatly decreased because of a better understanding of the epidemiology and microbiology of such injuries, leading to the development of clinical practice guidelines and targeted antibiotic drug therapy.

EPIDEMIOLOGY

It is estimated that 250,000 human bites, 400,000 cat bites, and 4.5 million dog bites occur each year in the United States in adults and children. Children are more likely than adults to sustain animal bites. Although only 10% of all bite wounds occur to the face, two-thirds of those wounds occur in children younger than 10 years of age. (2) Wounds in the extremities account for at least three-quarters of all bites, with the hand being the most common site. Wounds to the hand are most likely to become infected, and wounds to the face are least likely to become infected. In addition, puncture wounds are more likely to become infected than superficial wounds, lacerations, or wounds with obvious skin and soft tissue defects.

Cat bites are more evenly distributed among age groups, without a predisposition for one group in particular. Females are more likely to sustain cat bites than males. Injuries caused by cat bites seem to be less severe than most human or dog bites on first glance due to less skin and soft tissue destruction. Nonetheless, cat bites are more likely to have serious sequelae because they are small, deep puncture wounds that are difficult to cleanse. The infection rate for cat bites in the United States varies but can be up to 50%. (3)

The incidence of dog bites in children in developed countries is 1 to 3 per 1,000 children per year, which equates to nearly one-half to three-fourths of all dog bites of all ages. Males are twice as likely as females to sustain a dog bite injury. An average of 20 deaths associated with dog attacks are reported yearly in the United States. Sepsis and intracranial infections are the most common causes related to these deaths. Overall, approximately 20% of all dog bite wounds in US children become infected. (4)

The peak incidence of sustaining a dog bite occurs in the 5- to 9-year-old age group. (5) Preschool children are more likely to sustain bite injuries to their head and face, likely because their head is at mouth level of medium- and large-sized dogs. Nevertheless, children younger than 5 years of age are more likely to have attacks and injuries from smaller dogs. As a child gets older, injuries to the extremities become more common. In general, the child knows the owner of the dog in more than 75% of all bite wound cases. (2)

Bites from crossbred dogs account for most injuries because of their popularity among dog owners. However, a child's relative risk of injury is highest when interacting with German shepherd, pit bull, rottweiler, and Doberman breeds due to the sheer force that these dogs exert when biting. One study showed that the relative risk of an attack by a Doberman or German shepherd was approximately 5 times that of a Labrador retriever or crossbred species. (6) Another study evaluating 551 pediatric dog bite injuries in the United States found that pit bull terriers caused 51% of the injuries. Rottweiler was the second most common breed implicated in bite wounds at 9%. (7)

Paronychia is not considered specifically a bite wound because the mechanism of injury is different. This can occur when a child bites his or her own finger, but often it is secondary to a child obsessively sucking on his or her finger(s). Presence of a hangnail predisposes to paronychia. Because paronychia is caused by oral flora, it may be treated in a similar manner as human bite wounds.

Animal bites are a significant risk of transmission for rabies. In 2015, the 50 US states and Puerto Rico reported to the Centers for Disease Control and Prevention (CDC) 5,508 cases of animal rabies and 3 human cases. There are no documented cases of rabies in Hawaii. More than 90% of animal cases of rabies in the United States occur in wildlife, with bats being the animals with the highest percentage of cases (30.9%), followed by raccoons (29.4%), skunks (24.8%), and foxes (5.9%). Domestic animals accounted for only 7.6% of the cases. (8) Small rodents (rats, mice, squirrels, and hamsters) and lagomorphs (hares, pikas, and rabbits) rarely transmit rabies. Large rodents may pose a risk of transmission in areas where raccoon rabies is common.

Humans are incidental reservoirs of rabies, which is mainly an infection of other animals. In the United States, the number of human deaths caused by rabies has declined from 100 or more per year to 1 or 2 per year since the 1990s. This reduction in deaths happened mainly because of successful prophylaxis in domestic animals, especially among dogs, which are practically no longer a reservoir for rabies in the United States. According to data from the CDC, there were 23 cases of human rabies in the US states and Puerto Rico from January 2008 to September 2017. Eleven of these cases were indigenous, and the transmission was associated with bat exposure. There were 3 pediatric cases documented in this period: an 8-year-old who survived and had an unknown exposure; a 17-year-old who survived and had a bat exposure; and a 16-year-old who died and had a fox bite in Mexico. (8)

In contrast to the United States, exposure to rabid dogs accounts for more than 90% of human exposure and approximately 99% of human deaths caused by rabies worldwide. (8) Developing countries may have limited resources for reporting of rabies infections along with lack of public health programs directed to vaccination of stray dogs. Limited access to health-care and unavailability of rabies vaccine and immunoglobulin are significant factors that may contribute to such a high index of mortality.

Tetanus is another infection potentially caused by an animal or human bite. *Clostridium tetani* is ubiquitous in the environment and is commonly present in soil and both human and animal intestines. When present in a wound, the organism may replicate and produce toxins that are responsible for the characteristic tetanus infection. Cases of tetanus are significantly rare in the United States because of widespread routine immunization against it. In the United States there are reports of sporadic cases, and these occur mainly in adults with lack of immunization during childhood or inadequate boosters later in life. (9)

MICROBIOLOGY

Wound infections caused after any type of bite are usually polymicrobial in nature. Mixed aerobic and anaerobic bacteria from the mouth flora of the biting animal and the flora of the victim are commonly isolated in bite wound infections. An average of 5 different bacterial isolates per culture were reported in a series of infected wounds caused by dog and cat bites. (10)

Pasteurella spp. were the most frequent pathogens isolated in both types of animal bites (50% in dogs and 75% in cats). *Pasteurella* are facultative anaerobic gram-negative coccobacilli that grow on blood or chocolate agar. They are usual colonizers of the upper respiratory tract of many animal species. Dogs, cats, and other mammalians have high carriage rates of *Pasteurella* spp. in their oropharynx; therefore, a significant number of infections are caused by these microorganisms (Table 1). *Pasteurella canis* is the most common bacteria isolated in dog bites and *Pasteurella multocida* subspecies *multocida* in cat bites. (10)

Capnocytophaga canimorsus was identified as a pathogen causing severe infections in a series of 39 cases of bite wound infections. Dog bites caused infection in 56% of the cases from the same series, and 10% were associated with licking from the animal. Infections by *Capnocytophaga* pose a significant risk for sepsis in asplenic and immunocompromised children. (11)

Fusobacterium, Bacteroides, Prevotella, Propionibacterium, and *Peptostreptococcus* are other anaerobic bacteria recognized in isolates from bite wound cultures. *Eikenella corrodens* and *Streptococcus pyogenes* are more frequently associated with

TABLE 1. **Important Pathogenic Bacteria in Bite Wounds**

	TYPE OF BACTERIA	
TYPE OF BITE	**AEROBES**	**ANAEROBES**
Dog	*Pasteurella* spp. *Streptococcus* spp. *Staphylococcus* spp. *Capnocytophaga canimorsus*	*Fusobacterium* spp. *Bacteroides* spp. *Prevotella* spp. *Porphyromonas* spp. *Propionobacterium* spp. *Peptostreptococcus* spp.
Cat	*Pasteurella* spp. *Streptococcus* spp. *Staphylococcus* spp. *Moraxella* spp.	*Fusobacterium* spp. *Bacteroides* spp. *Porphyromonas* spp. *Prevotella* spp. *Propionobacterium* spp.
Human	*Streptococcus* spp. *Staphylococcus* spp. *Eikenella corrodens* *Haemophilus* spp.	*Fusobacterium* spp. *Prevotella* spp. *Peptostreptococcus* spp. *Veillonella* spp.

human bites. *Streptococcus pyogenes* was identified in cultures from dog bites but in none of the cultures from cat bites. Streptococci, *Staphylococcus aureus, Moraxella catharralis, Neisseria* spp., and *Corynebacterium* are other common aerobic bacteria found in infected dog and cat bites. *Staphylococcus aureus* causes infection more frequently in dog bites than in cat bites. (11)

Cultures from human bites are usually mixed with aerobic and anaerobic bacteria. *Streptococcus anginosus, Streptococcus pyogenes, S aureus, E corrodens,* and *Haemophilus* spp. are aerobic bacteria commonly isolated from human bites. *Eikenella corrodens* is a gram-negative rod frequently associated with wound infections caused by clenched-fist injuries. This pathogen is susceptible to penicillin but exhibits resistance to first-generation cephalosporins and β-lactamase–stable penicillins. *Prevotella* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., *Bacteroides* spp., and *Veillonella* spp. are anaerobic bacteria frequently isolated in wounds from human bites. (12)

More severe infections and greater morbidity are associated with anaerobic bacteria cultured from wounds sustained by human bites compared with animal bites. Most of these anaerobes are β-lactamase producers, thus the importance of choosing adequate empirical antibiotic coverage with a β-lactamase inhibitor. Cultures from paronychia report similar microbiologic pathogens as wounds caused by human bites, although the mechanism of injury is different, as described previously.

Etiologic agents from bites of species other than dogs, cats, and humans, are not well described in the medical literature. Infections with *Pasteurella* spp. have been described in bites by large felines such as tigers and leopards. *Pseudomonas* spp., *Aeromonas hydrophila,* and *Clostridium* spp. have been isolated in infections from catfish, eel, and reptiles. (12)

Both human and animal bites have the potential to transmit pathogens that cause systemic infections. Tetanus, rabies, *Bartonella* (cat-scratch disease), tularemia, brucellosis, leptospirosis, and rat-bite fever may be transmitted through an animal bite. Insects such as ticks, flies, and mosquitoes have the potential to carry and transmit significant viral, bacterial, fungal, and parasitic sources of infection. Human bites may transmit important pathogens, such as hepatitis B and C virus, cytomegalovirus, and herpesvirus. Transmission of human immunodeficiency virus through human bites is extremely rare; however, it is biologically possible, and a few cases have been reported (Table 2). (13)

CLINICAL MANIFESTATIONS

Patients who experience an animal bite wound can show signs and symptoms of infection within hours to days after the initial injury. Manifestations suggestive of infection include pain, erythema, and swelling of the affected area. Serosanguineous or purulent drainage may or may not be present. Most individuals are afebrile at the time of evaluation. Lymphadenitis or lymphangitis is present in 20% of patients or less.

Patients infected with *P multocida* secondary to an animal bite tend to experience intense pain, swelling, and erythema within 12 to 18 hours of sustaining an injury. (14) In comparison, patients with a staphylococcal or streptococcal infection tend to develop less intense symptoms over days

TABLE 2. **Other Systemic Infections Transmitted by Human and Animal Bites**

ANIMAL TYPE	INFECTIONS
Dog	Leptospirosis (*Leptospira* spp.) Tetanus *(Clostridium tetani)* Tularemia *(Francisella tularensis)* Rabies (rabies virus)
Cat	Cat-scratch disease *(Bartonella* spp.) Tularemia *(F tularensis)* Sporotrichosis *(Sporothrix* spp.) Rabies (rabies virus)
Human	Hepatitis B (hepatitis B virus) Hepatitis C (hepatitis C virus) Cytomegalovirus infection Herpes (herpes simplex virus) Syphilis *(Treponema pallidum)* Human immunodeficiency virus infection
Rat	Rat-bite fever *(Streptobacillus moniliformis* or *Spirillium minus)* Leptospirosis *(Leptospira* spp.)
Rodents	Leptospirosis *(Leptospira* spp.) Tularemia *(F tularensis)*
Bat Ferret Raccoon Fox	Rabies (rabies virus)

rather than hours. In addition, the cellulitis caused by staphylococci or streptococci is more diffuse and typically less severe than that seen with *P multocida* infections.

Complications of animal bites other than cellulitis must be kept in mind when evaluating human and animal bites. Osteomyelitis, tenosynovitis, tendinitis, orbital cellulitis, or brain abscesses can occur. Signs and symptoms of osteomyelitis include persistent pain, swelling, and erythema of the infected site in addition to tenderness to palpation of a bony structure near the bite site. Tenosynovitis also involves persistent pain, swelling, and erythema of the infected site in addition to tenderness to palpation of a bony structure near the bite site. Tenosynovitis also involves persistent pain, swelling, and erythema but instead of bony tenderness there is often a mass overlying an infected tendon sheath. Brain abscesses and meningitis should be kept in mind when evaluating children with perforating cranial bites because these can prove to be fatal complications.

Of all human bites, clenched-fist injuries are the most serious because they can lead to severe sequelae. These injuries are sustained when one person uses a closed fist to strike another person in the teeth, leading to a break in the skin over the knuckles. The injury most commonly affects the metacarpophalangeal joint of the third digit of the dominant hand. (13) The seriousness of clenched-fist injuries is often overlooked because the initial injury typically does not appear significant. Bacteria that entered through the broken skin over the knuckle can be carried to the tendons proximally as a person relaxes the hand from a closed to an open position. This potentiates the spread of bacteria to the deeper surfaces of the hand. In addition, the joint capsule or bone is frequently involved with this type of injury. Given these features, patients with clenched-fist injuries are at high risk for septic arthritis, osteomyelitis, tenosynovitis, tendinitis, joint stiffness, or permanent limited range of motion, prompting the need for immediate antibiotic drug treatment. Patients with clenched-fist injuries usually seek medical care due to signs and symptoms of infection within 8 hours of sustaining the injury.

Patients with infected human bites, including clenched-fist injuries, present with similar manifestations as infected animal bites, including pain, tenderness, and erythema of the affected site with or without serosanguineous or purulent drainage. Paronychia presents with the same symptoms as any bite wound infection of the hand. Fever, lymphadenitis, and lymphangitis are rarely present. Infection of the hand typically spreads proximally up the arm, as opposed to distally. Complications of non–clenched-fist injuries include compartment syndrome and nerve injury, in addition to osteomyelitis, septic arthritis, tenosynovitis, and tendinitis. However, these complications are seen less commonly than with clenched-fist injuries.

MANAGEMENT

Management of human and animal bites should include measures to provide appropriate care of the wound in the immediate period of the injury and adequate actions targeted to identify and minimize the risk of infections or other serious complications. We propose the following stepwise approach based on our review of the literature (Table 3):

1. History. Obtain a pertinent clinical history to help with the decision-making process for actions regarding initial wound care, including the need for active or passive immunizations, indications for obtaining cultures that would help determine specific pathogens, indications for antibiotic prophylaxis versus empirical therapy, and establishment of an adequate disposition for the patient.
2. Evaluation. Perform an initial assessment of the patient with particular emphasis on the clinical status of the child and the location, extension, characteristics, and severity of the wound. Obtain appropriate imaging tests to visualize structures that are at risk for being affected.

3. Wound management. Practice adequate cleansing of the wound and identify indications for immediate closure versus delayed closure and watchful monitoring. Obtain cultures if indicated.
4. Medications. Follow indications for active and/or passive immunizations based on the child's history. Choose appropriate antibiotics for empirical coverage when indicated for prophylaxis or for treatment of infection (Tables 3 through 5, Fig).
5. Disposition. Establish appropriate disposition for the child. Determine whether the child requires hospital admission or management as an outpatient with adequate follow-up.

ANTIMICROBIAL THERAPY

There are limited data about specific recommendations for antibiotic prophylaxis for animal bites. However, the Infectious Diseases Society of America guidelines state that for soft tissue and skin infection it is recommended to prescribe preemptive antibiotic agents for patients who are immunocompromised and those who are asplenic; for patients with advanced liver disease; for patients with moderate to severe puncture wounds, especially injuries that may have penetrated the bone, tendon, or joint capsule; and for facial, hand, foot, or genitalia bites. Duration of preemptive therapy may be up to 3 to 5 days, but all children with bite wounds need to be reevaluated within 24 to 48 hours to monitor for signs and symptoms of infection. (15) For soft tissue infection, a 7- to 10-day course of antibiotic therapy may be sufficient. However, the final duration of therapy depends on the location and severity of the wound and the patient's clinical response. A 10- to 14-day course of antibiotics is indicated for more severe infections and should be extended for 4 to 6 weeks in the presence of bone and joint infections. (15)

Optimal selection of empirical antibiotic agents should be based on the most common pathogens according to the type of bite (eg, animal or human), the location of the wound (eg, hand, face, skull), and the possible patterns of resistance expressed by the bacteria. In general, an adequate antibiotic regimen should provide coverage for the potential pathogenic aerobic and anaerobic flora from the mouth of the animal or human inflicting the bite. Some experts recommend antibiotic prophylaxis in mild dog bites managed in a medical facility 8 hours after the event and for all moderate to severe dog bites seen less than 8 hours after the event with particular attention to the presence of edema or signs of crush injury. (16)

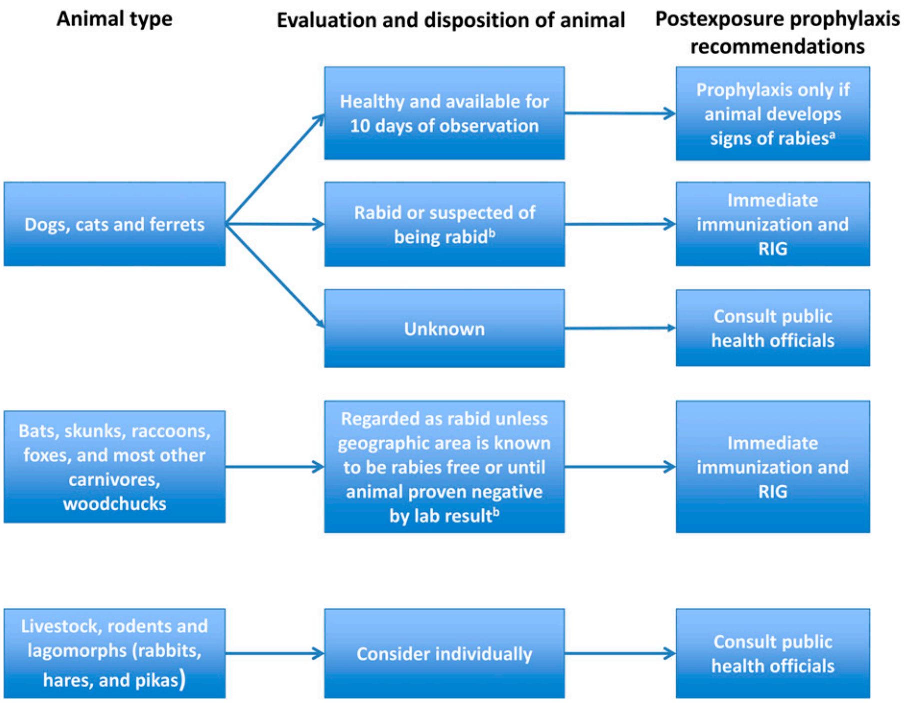

Animal type
Evaluation and disposition of animal
Postexposure prophylaxis recommendations
Healthy and available for 10 days of observation
Prophylaxis only if animal develops signs of rabies^{a}
Dogs, cats and ferrets
Rabid or suspected of being rabid^{b}
Immediate immunization and RIG
Unknown
Consult public health officials
Bats, skunks, raccoons, foxes, and most other carnivores, woodchucks
Regarded as rabid unless geographic area is known to be rabies free or until animal proven negative by lab result^{b}
Immediate immunization and RIG
Livestock, rodents and lagomorphs (rabbits, hares, and pikas)
Consider individually
Consult public health officials

Figure. Rabies postexposure prophylaxis. [a]Prophylaxis of the exposed child should be started with rabies immune globulin (RIG) and vaccine at the first sign of rabies in the biting animal. [b]The animal should be euthanized and tested as soon as possible. Observation is not recommended for these types of animals. Immunization is discontinued if there are negative immunofluorescent test results from the animal. (Adapted with permission from American Academy of Pediatrics. Rabies. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:658–666.)

TABLE 3. **General Management of Bite Wounds**

MEASURE	ACTION
History	Animal • Type of animal • Health of the animal • Attack provoked versus unprovoked • Human bite (health status of the person inflicting the bite [HIV, HBV, HCV]) Patient • High-risk patient? Immunocompromised, asplenic • Immunization status of the patient (tetanus, HBV)
Evaluation	• Vital signs and clinical assessment • Location and depth of the wound • Type of wound (puncture, abrasion, avulsion, laceration) • Extent of the wound, edema, erythema, foreign material present, purulent discharge • Neurovascular examination
Initial management	• Hibiclens or povidone-iodine should not be used • Do not irrigate puncture wounds • Irrigate wounds other than puncture using splashguard shields with ≥250 mL of normal saline. If not available use an 18-gauge catheter or needle attached to a 30- or 60-mL syringe • Based on clinical suspicion may obtain pertinent diagnostic imaging to rule out foreign material • Perform debridement and removal of foreign material • Obtain wound cultures if evaluation occurs >8 h after the event or if the wound has signs of infection
Wound closure	• Early primary closure for wounds of the face and neck • Primary closure of wounds from animal bites may be appropriate if none of the following are met: ✓ Wounds in the hand should be left open. Consider consultation with a hand surgeon. Clenched-fist injury should be evaluated by a surgeon ✓ Wounds with signs of infections should not be closed ✓ Closure is not recommended in high-risk wounds if >8 to 12 h have elapsed from the time of the injury • Subcutaneous sutures should not be used
Prophylaxis	• Determine indications for rabies and tetanus prophylaxis • Prescribe antibiotics if: ✓ Immunocompromised or asplenic ✓ Moderate to severe puncture wounds ✓ Injuries to the bone, joint capsule, or tendons ✓ Wounds in the face, hand, or genital area
Follow-up	• Wound inspection within 48 h

HBV=hepatitis B virus, HCV= hepatitis C virus, HIV=human immunodeficiency virus.

Bites in the skull of a young infant or toddler may cause penetrating injury to cranial contents; thus, special considerations should be made for antibiotic agents that not only cover for the most likely pathogens but also penetrate the blood-brain barrier appropriately. Intravenous third-generation cephalosporins plus metronidazole, or meropenem alone should be considered for these types of injuries, with the possible addition of vancomycin if there are concerns about methicillin-resistant *S aureus* (MRSA) infection. A multidisciplinary approach with surgical services and infectious diseases consultation is recommended.

The oral agent amoxicillin-clavulanate provides adequate coverage for aerobic bacteria such as streptococci, methicillin-susceptible *S aureus*, *Pasteurella*, and *E corrodens*. It also covers oral anaerobic bacteria known to have β-lactamase–producing activity, such as *Prevotella* and *Porphyromonas* spp. In children with serious allergic reactions (anaphylaxis, wheezing, angioedema, or urticaria) to penicillin, an extended-spectrum oral cephalosporin (cefpodoxime) or trimethoprim-sulfamethoxazole plus clindamycin is an alternative. (15)

Ampicillin-sulbactam is the intravenous agent of choice when parenteral therapy is indicated. Piperacillin-tazobactam may be used as an alternative. Neither agent provides coverage for MRSA, and adding vancomycin in cases of severe infection may be considered while waiting for the culture results. An optimal empirical antibiotic regimen for children with allergic reactions to penicillin should include an extended-spectrum cephalosporin (ceftriaxone, cefotaxime) or trimethoprim-sulfamethoxazole, in addition to clindamycin, or meropenem alone. Adding vancomycin

TABLE 4. Empirical Antibiotics for Human or Animal Wounds

TYPE OF BITE	ORAL	PARENTERAL	PENICILLIN ALLERGY ORAL	PENICILLIN ALLERGY PARENTERAL
Dog, cat, human	Amoxicillin-clavulanate	Ampicillin-sulbactam	Extended-spectrum cephalosporin or trimethoprim-sulfamethoxazole PLUS clindamycin	Extended-spectrum cephalosporin or trimethoprim-sulfamethoxazole PLUS clindamycin OR carbapenem

(Adapted with permission from American Academy of Pediatrics. Bite Wounds In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases. *30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:205–210.)*

for coverage of MRSA in severe infections should be considered when meropenem is used alone and cultures are pending.

Parenteral or oral extended-spectrum cephalosporins do not provide adequate coverage against some anaerobes, so they should not be used empirically as monotherapy. First-generation cephalosporins do not provide coverage for *E corrodens* and some anaerobes and, therefore, are not recommended as empirical therapy. Doxycycline is an alternative agent that provides coverage of gram-positive aerobic bacteria, including MRSA and the gram-negative rod *Pasteurella*. Azithromycin is a macrolide that shows good in vitro activity against pathogens that commonly cause bite wound infections, but clinical data are lacking to recommend it as a first-line agent. Fluoroquinolones show activity against *P multocida* and some anaerobes. These agents are not approved for this indication in children, but they may be considered in cases of severe infections with susceptible organisms.

Management of tetanus prophylaxis in bite wounds should follow recommendations according to the immunization status of the affected person. When the child has received fewer than 3 doses of adsorbed tetanus toxoid–containing vaccine or the status is unknown, human tetanus immune globulin should be administered along with a dose of age-appropriate tetanus toxoid–containing vaccine. Equine antitoxin may be available in countries where tetanus immune globulin is not. Equine antitoxin is no longer available in the United States. See Table 5 for specific recommendations of tetanus prophylaxis in those who had previously received at least 3 doses of tetanus vaccine. (9)

The animal species is important in determining the risk of rabies exposure. It is encouraged to contact local public health authorities for determining risk. Use of passive and active prophylaxis is ideal once wound care is completed and assessment of the risk warrants postexposure prophylaxis. See the Figure for recommendations for rabies prophylaxis. Rabies prophylaxis should be initiated as soon as possible. Children who have previously completed vaccination regimens or have documented protecting rabies antibody titers should receive only vaccine booster in case of new exposure. Two vaccines are available for use in the United States: human diploid cell vaccine and purified chicken embryo cell vaccine. Unvaccinated immunocompetent children should

TABLE 5. Tetanus Prophylaxis in Bite Wounds

RECEIVED DOSES OF ADSORBED TETANUS TOXOID	ADMINISTER DTaP, Tdap, OR Td[a]	ADMINISTER TIG[b]	
<3 doses or unknown		Yes	Yes
≥3 doses	<5 y since last tetanus toxoid–containing vaccine	No	No
	≥5 y since last tetanus toxoid–containing vaccine	Yes	No

DTaP=diphtheria and tetanus toxoid and acellular pertussis vaccine, Td=adult-type diphtheria and tetanus toxoid vaccine, Tdap: booster tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, TIG=tetanus immune globulin (human).

[a] *DTaP for children younger than 7 years. Tdap preferred for underimmunized children 7 years or older who have not received Tdap previously.*

[b] *Intravenous immunoglobulin should be used if TIG is not available.*

(Adapted with permission from American Academy of Pediatrics. Tetanus (lockjaw). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases. *30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:773–778.)*

receive a 4-dose series of rabies vaccines along with a dose of human rabies immune globulin for postexposure prophylaxis. Rabies immune globulin should be infiltrated around the wound, and it should be given on day 0 only. The first dose of rabies vaccine should be followed by 3 subsequent doses of rabies vaccine alone on days 3, 7, and 14 after the first dose. (17) Laboratory work should be obtained to determine antibody protection 7 to 14 days after administration of the last dose. (18)

CONCLUSION

All things considered, animal bites are usually preventable injuries. Clinicians caring for children should investigate what kind of pets the child is exposed to, inquiring particularly about specific breeds of dogs and whether the animals are up to date on immunizations. The American Academy of Pediatrics (AAP) Committee on Infectious Diseases discourages the acquisition and ownership of nontraditional pets in households with young children. Both the AAP and the CDC have parent-friendly tips to prevent animal bites, particularly dog bites. This information should be discussed with the family when possible, and it should be provided to them at the end of a health supervision visit. There are no data to support this action, but we encourage it for primary care practitioners due to the continuously increasing number of pet animals as well as companion and service animals. School-aged children should be included in the discussion about pet safety throughout a health supervision visit. As a final point, the AAP Committee on Infectious Diseases also states that "pediatricians, veterinarians, and other health care professionals are in a unique position to offer advice on proper pet selection, to provide information about safe pet ownership and responsibility, and to minimize risks to infants and children." (18)

Summary

- On the basis of expert consensus due to lack of evidence, primary wound closure for animal bite wounds is recommended only for those to the face. (16)
- On the basis of expert consensus due to lack of strong evidence, from Infectious Diseases Society of America Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: "preemptive antibiotic therapy for 3 to 5 days is recommended for patients who are immunocompromised; are asplenic; have advanced liver disease; have preexisting or resultant edema of the affected area; have moderate to severe injuries, especially to the hand or face; or have injuries that may have penetrated the periosteum or joint capsule." (16)
- On the basis of expert consensus and moderate evidence, amoxicillin-clavulanate is the antibiotic of choice for prophylaxis or empirical treatment of an animal or human bite. (15)
- On the basis of expert consensus due to the lack of evidence, postexposure prophylaxis for rabies and tetanus may be indicated. (16)

Take Home Points

- Health-care providers caring for children have a duty to inquire about what kinds of pets the child is frequently exposed to and the immunization status of the animal.
- Health-care providers have the responsibility to counsel families on pet safety.
- Nontraditional pets pose a potential risk of infection and injury, especially for young children and the immunocompromised.
- The American Academy of Pediatrics Committee on Infectious Diseases states that children should be counseled "to never handle unfamiliar, wild, or domestic animals, even if animals appear friendly."
- Health-care providers should counsel families on avoiding ownership or adoption of wild pets or even bringing wild pets into their homes.
- Children should always be supervised when interacting with animals, particularly if they are younger than 5 years of age.
- Amoxicillin-clavulanate is the antibiotic of choice for prophylaxis or empirical treatment of an animal bite.
- Clindamycin plus trimethoprim-sulfamethoxazole is an acceptable alternative for those with penicillin allergies.
- Reviewing tetanus immunization status in a child sustaining an animal bite is an important opportunity to encourage being up to date with the immunization schedule.
- Assessing risk for rabies exposure depending on the nature of the animal inflicting the bite is a key factor to preventing a fatal outcome.

Suggested Areas for Quality Improvement Projects

- Implementation of anticipatory guidance in the health supervision visit regarding animal safety
- Development of standard policies for service animals versus companion animals
- Creation of order sets in electronic health record systems in emergency department and acute care centers aimed to guide practitioners regarding management of human and animal bite wounds

Suggested Websites

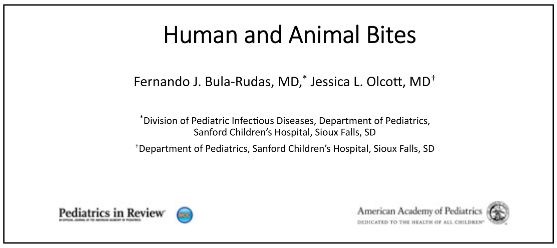
AAP: Dog Bite Prevention Tips 2017 https://www.aap.org/en-us/about-the-aap/aap-press-room/news-features-and-safety-tips/Pages/Dog-Bite-Prevention-Tips-2017.aspx Accessed April 26, 2018.

CDC: Preventing Dog Bites https://www.cdc.gov/features/dog-bite-prevention/index.html Accessed April 26, 2018.

CDC: Zoonotic Diseases https://www.cdc.gov/zoonotic/gi/ Accessed April 26, 2018.

The Humane Society of the United States http://www.humanesociety.org/animals/pets/?credit=web_id93480558 Accessed April 26, 2018.

To view teaching slides that accompany this article, visit http://pedsinreview.aappublications.org/content/39/10/490.supplemental.



Human and Animal Bites

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1. Which of the following healthy and fully immunized 5-year-old girls is most likely to develop bacterial infection at the site of an animal bite?
    - A. Home pet cat bite to the face.
    - B. Home pet dog bite to the face.
    - C. Neighbor pet cat bite to the hand.
    - D. Neighbor pet dog bite to the thigh.
    - E. Provoked dog bite to the face from an unknown dog.
2. A previously healthy and fully immunized 8-year-old girl is brought to the office with a 1-day history of increasing erythema and pain after a dog bite to her right arm that occurred 3 days earlier from a friend's pet dog. On examination her temperature is 98.9°F (37.2°C) and her other vital signs are normal. There is a 5 × 8-cm area of erythema of her right forearm surrounding the bite wound with a small amount of serosanguinous drainage. The drainage is swabbed and sent for culture. Which of the following organisms is most likely to grow from the culture?
    - A. *Clostridium tetani.*
    - B. *Eikenella corrodens.*
    - C. *Pasteurella canis.*
    - D. *Streptococcus anginosus.*
    - E. *Streptococcus pyogenes.*
3. A previously healthy 16-year-old boy is brought to the emergency department with increasing pain and redness of his right hand over the past 6 hours. He was in a fight at school yesterday and hit his classmate in the teeth with his closed fist and had a laceration over his third and fourth knuckles. He is afebrile and there is tenderness, swelling, and erythema of the dorsum of his right hand. There is no lymphangitis. Which of the following is the most likely pathogen(s)?
    - A. *Aeromonas hydrophila.*
    - B. *Bacillus subtilis.*
    - C. *Capnocytophaga canimorsus.*
    - D. Mixed aerobic and anaerobic bacteria.
    - E. *Streptococcus pyogenes* and *Streptococcus agalactiae.*
4. For the same boy in question 3, which of the following is the most likely complication of his infection?
    - A. Compartment syndrome.
    - B. Nonsuppurative lymphadenitis.
    - C. Suppurative lymphadenitis.
    - D. Tenosynovitis.
    - E. Toxic shock syndrome.
5. A 6-year-old girl with sickle cell disease is brought to the immediate care clinic after a cat bite to the dorsum of her left foot 2 hours earlier from a friend's pet cat. She is not currently taking any antibiotics, and she has no known allergies. She received the recommended immunizations at 5 years of age. Her examination findings are normal except for a puncture wound on the dorsum of her left foot without drainage or surrounding erythema. The wound is cleansed. Which of the following is the most appropriate next step in management?
    - A. Administer tetanus immune globulin and tetanus toxoid vaccine.
    - B. Administer tetanus toxoid vaccine.
    - C. Magnetic resonance imaging of her foot.
    - D. Preemptive amoxicillin-clavulanate.
    - E. Wound care only with soap and water.

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Collagen Vascular Diseases: SLE, Dermatomyositis, Scleroderma, and MCTD

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Practice Gap

Timely and accurate recognition of collagen vascular disorders (CVDs), and implementation of effective screening and referral processes for patients suspected of having a CVD, remain a challenge for many physicians. The result, too often, is unnecessary testing and referrals, and in some cases unnecessary anxiety for physicians, patients, and parents.

Objectives

After completing this article, readers should be able to:

1. Recognize the common clinical symptoms and signs of systemic lupus erythematosus, dermatomyositis, and scleroderma, and their distinction from common infectious mimics.
2. Recognize the testing that can clarify the likelihood of whether a child has a rheumatic disease, including the limited utility of early serologic testing for autoantibodies.
3. Recognize the prognosis and management objectives for these often-chronic disorders, and practical steps to ensure excellent outcomes.

AUTHOR DISCLOSURE Drs Vehe and Riskalla have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ANA	antinuclear antibody
CTD	connective tissue disease
CVD	collagen vascular disease
dsDNA	doubled-stranded DNA
DM	dermatomyositis
ENA	extractable nuclear antigen
JIA	juvenile idiopathic arthritis
MCTD	mixed connective tissue disease
NFC	nail fold capillary
RA	rheumatoid arthritis
RF	rheumatoid factor
RP	Raynaud phenomenon
RNP	ribonucleoprotein
SLE	systemic lupus erythematosus

INTRODUCTION

Timely and accurate recognition of collagen vascular diseases (CVDs), and implementation of effective screening and referral processes for patients suspected of having a CVD, remain challenging for many physicians. The result, too often, is unnecessary testing with questionable results, leading in some cases to unnecessary referrals and anxiety for physicians, patients, and parents. (1)

Sometimes, CVDs are also referred to as connective tissue diseases (CTDs), but neither name fully captures their essential nature. These are not primarily heritable disorders affecting collagen-containing structures, or disorders of vascular development, but rather are immune-mediated inflammatory diseases. The immunologic targets vary, but the inflammatory disease often affects collagen-containing tissues, including the musculoskeletal system and many other tissues. The targeting of blood vessels can lead to manifestations ranging from reversible vasospasm of Raynaud phenomenon (RP) to vascular injury of 1 or more organ systems, often with serious consequences.

The diseases that are classically included under the heading of CVDs/CTDs for adults include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, dermatomyositis (DM) and polymyositis, scleroderma, mixed connective tissue disease (MCTD), and many forms of idiopathic vasculitis. For the purposes of this review, the focus will be on SLE, DM, and scleroderma, with mention also of RP and MCTD. Any references to RA are specific to the adult disease and the childhood equivalent termed "rheumatoid factor (RF)–positive juvenile idiopathic arthritis (JIA)." Due to past confusion over the relationship between a specific disease in adults termed "rheumatoid arthritis" and a group of diseases in children termed "juvenile rheumatoid arthritis," the preferred term for the group of diseases in children is now "juvenile idiopathic arthritis." Few children (<10%) with JIA have the childhood equivalent of RA.

CLINICAL APPROACH

The approach to rheumatic diseases is similar to that for other medical problems, namely, use of a thorough history and physical examination to help the clinician quickly identify the most likely diagnostic possibilities and focus diagnostic testing. The starting point is a general comprehensive health history and problem list, followed by a detailed history of any new medical concerns. The health history is followed by a comprehensive physical examination, with additional focus on the new medical concerns. A focused examination that accurately characterizes the abnormal findings of involved areas can greatly streamline the evaluation process.

On completion of a detailed and specific problem list based on the medical history and physical examination, the next steps in the evaluation and management become clearer. In some cases, no additional studies, such as imaging or laboratory tests, are needed. However, in the case of CVDs/CTDs, which are often complex in their manifestations, imaging and laboratory tests are commonly needed. Sometimes a quick phone consultation with a rheumatologist can actually simplify the process. Although this step might seem more time-consuming, a well-constructed and communicated diagnostic and treatment plan will help the physician, patient, and parents quickly feel confident that they are on the right path.

CASE EXAMPLE PART 1: INITIAL PRESENTATION

A previously well 10-year-old girl noted that, on exposure to the winter cold, her fingers would tingle and then blanch to white, recover to a bluish cold, and when rewarmed would become bright red and sting. This circulatory problem was less apparent as summer approached, but then she began having increased fatigue, shortness of breath with sports that was not improved with an inhaled bronchodilator, and an inability to fully extend her elbows. After the start of school in the fall she began having recurrent fevers and sore throats, but throat cultures were repeatedly negative. A scaly red rash appeared on her face and was partially responsive to topical glucocorticoid treatment. Her appetite unexpectedly dropped off and her weight plateaued.

On physical examination she had a distinctly erythematous and scaly rash on her cheeks, chin, and ears. Similar erythema and scale was present on the extensor side of the finger joints, mixed with scattered atrophic areas. She had a symmetrical polyarthritis affecting the elbows, wrists, fingers, knees, and toes. Features of the arthritis for many joints included swelling and loss of range of motion associated with pain at the limits of motion. The larger joints were unusually warm to the touch. Magnified inspection (with an otoscope or a dermatoscope) of the skin folds (eponychium) proximal to her fingernails showed that the nail fold capillaries (NFCs) were thickened and irregular. (2)

The diagnostic considerations for this patient are many, but the problem list quickly suggests a narrow list of possible CVDs/CTDs. This patient's problem list included the following:

- Fatigue, impaired activity level, impaired weight gain, shortness of breath, recurrent fever, and recurrent nonstreptococcal pharyngitis
- Digital vasospasm with abnormal NFCs
- Rashes of the face, ears, and hands with erythema, scale, and some atrophy
- Symmetrical polyarthritis

The first distinguishing feature for this child is her history of digital vasospasm associated with abnormal NFCs. Reversible vasospasm of distal arterial vessels is a feature of RP. This vasospasm is most commonly triggered by cold or other stresses, and it can occur as a primary process or as a secondary process associated with several CVDs/CTDs. Although classically defined as being triphasic, not all patients go through 3 discrete phases. (3) With vasospasm, the digit exhibits a distinctly demarcated distal pallor (Fig 1) and coolness, and then progresses through a cool dusky bluish phase and/or a bright hyperemic flush. Sensory changes, including pain and burning, may occur but are not always present during the phases of restricted blood flow and flushing.

Raynaud phenomenon is labeled as primary when it occurs in isolation or as secondary when it occurs in association with a

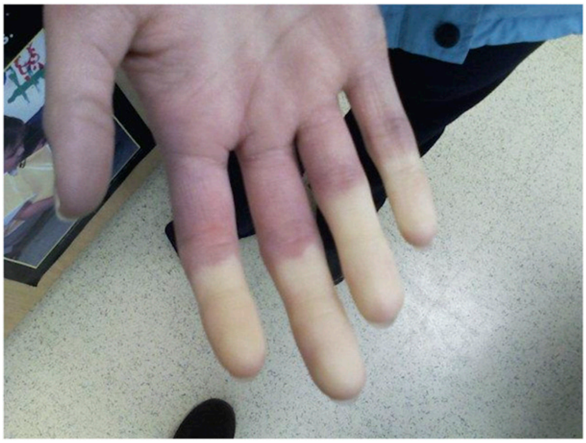

Figure 1. Raynaud phenomenon, ischemic phase, with an abrupt line of demarcation of nonperfused skin.

CVD/CTD. Secondary RP, but not primary RP, may feature distinctly abnormal NFCs. The capillaries are normally barely visible and fine in caliber as they extend to the end of the skin (Fig 2A), but with inflammatory vascular disease there may be progressive changes in the caliber and shape of the capillaries, including thickening, irregularity, and even occlusion with capillary dropout (Fig 2B). Primary RP is often confused with acrocyanosis, a condition in which individuals have constitutionally cool hands or feet. With acrocyanosis, the autonomic regulation of superficial blood flow leads the skin of the distal extremities to be naturally cool and dusky in color. With cold exposure the skin can become somewhat pale, but in contrast to RP there will not be a discretely demarcated distal pallor. Just as NFC changes are not a feature of primary RP, they are also not a feature of acrocyanosis. The CVDs/CTDs with which NFC changes are most common are SLE, DM, scleroderma, and MCTD.

The second distinguishing feature for this child is the prominent facial rash, for which some of the same diagnoses on this short list of CVDs/CTDs are the primary considerations. Let's further review each of these possibilities.

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition

Systemic lupus erythematosus is commonly described as one of the clearest examples of autoimmunity that exhibits florid laboratory evidence of inappropriate immune activation and can cause damage to almost any part of the body, from head to toe. The variability of its manifestations is a source of much confusion, and any 2 individuals can differ vastly in the presentation and evolution of their disease.

Epidemiology

The epidemiology of SLE is still an area of active research, and estimates of its prevalence are highly variable, with an upper limit of approximately 1 million individuals in the United States with SLE. This disorder predominantly affects adults (80%–90%), predominantly females (≥90%), and is most common above age 10 years, but there are tremendous differences in prevalence and severity among different groups. On average it tends to be more common and more severe in its manifestations for nonwhite groups, including people of African, Asian, and Hispanic ancestry, and it is not unusual for there to be a family history of SLE.

Pathogenesis and Presentation

Systemic lupus erythematosus features activation of innate and adaptive immune systems, including humoral and cellular immunity. Interferon-α seems to be a key driver of this immune overactivity. Although a generalized hypergammaglobulinemia is common, overproduction of specific autoantibodies is nearly universal. Complement activation plays a major role in many of its manifestations, and depletion of serum levels of C3 and C4 is common during active disease. Deposits of complement components can be found on immunofluorescence studies of many affected tissues.

The presentation of SLE can be acute or insidious, initially affecting a single organ system or presenting with

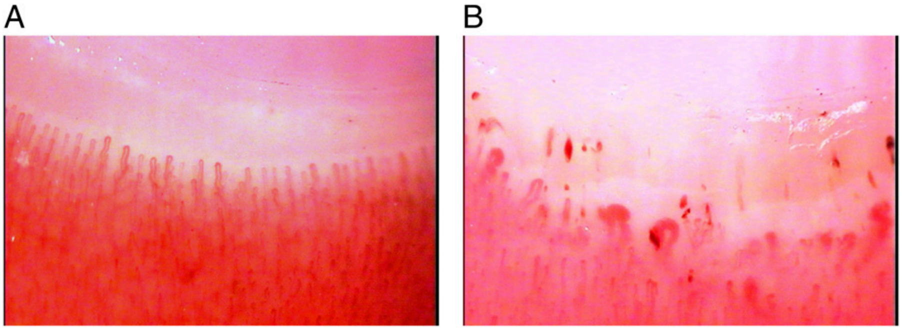

Figure 2. A. Normal fine nail fold capillaries as seen on capillary microscopy. (4) B. Abnormal nail fold capillaries, including microhemorrhages, dilated capillaries, megacapillaries, and avascular areas, as noted by the authors. (4)

multisystem disease, but often includes intrusive constitutional symptoms. The symptoms and signs can present asynchronously, and careful consideration of past and present problems helps with identification of SLE as a possible diagnosis that warrants further evaluation. Although the initial problem can even be relatively minor, such as a mild RP, children with SLE often have fast progression of worsening disease features and are commonly diagnosed within 6 to 12 months of onset of the original symptoms.

Since the spectrum of manifestations is so diverse, a good starting point for thinking about SLE is to consider the descriptors in the 1997 American College of Rheumatology classification criteria (Table 1) or the 2012 Systemic Lupus International Collaborating Clinics criteria (Table 2). Although these are not meant to be followed rigidly as diagnostic criteria, they are helpful for recognizing discriminating features of SLE; for focusing the review of the patient's medical history, physical

TABLE 1. ACR Criteria for the Classification of SLE

	CRITERION	DEFINITION
1	Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2	Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3	Photosensitivity	Skin rash as a result of an unusual reaction to sunlight, by patient history or physician observation
4	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5	Arthritis	Nonerosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling, or effusion
6	Serositis	A. Pleuritis-convincing history of pleuritis pain or rub heard by a physician or evidence of pleural effusion OR B. Pericarditis documented by ECG or rub or evidence of pericardial effusion
7	Renal disorder	A. Persistent proteinuria >0.5 per day or >3+ if quantitation not performed OR B. Cellular casts, may be red blood cell, hemoglobin, granular, tubular, or mixed
8	Neurologic disorder	A. Seizures, in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance, OR B. Psychosis, in the absence of offending drugs or known metabolic derangements, eg, uremia, ketoacidosis, or electrolyte imbalance
9	Hematologic disorder	A. Hemolytic anemia, with reticulocytosis OR B. Leukopenia, <4,000/mm total on ≥2 occasions OR C. Lymphopenia, <1,500/mm on ≥2 occasions OR D. Thrombocytopenia, <100,000/mm in the absence of offending drugs
10	Immunologic disorder	A. Anti-DNA: antibody to native DNA in abnormal titer OR B. Anti-Sm: presence of antibody to Sm nuclear antigen OR C. Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for ≥6 mo and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11	Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with drug-induced lupus syndrome

The criteria are cumulative and need not be present concurrently. The patient may be classified as having SLE with 4 of 11 criteria. ACR=American College of Rheumatology, ECG=electrocardiography, IgG/IgM=immunoglobulin G/M, SLE=systemic lupus erythematosus.

Adapted with permission from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. *1982;25(11):1271–1277 (5) and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus.* Arthritis Rheum. *1997;40(9):1725. (6)*

TABLE 2. **SLICC Criteria for the Classification of SLE**

The criteria are cumulative and need not be present concurrently. A patient may be classified as having SLE with either:

1. Four of the clinical and immunologic criteria, including ≥1 clinical criterion and 1 immunologic criterion, or

2. Biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies

Clinical criteria:

1. Acute cutaneous lupus, including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis OR subacute cutaneous lupus
2. Chronic cutaneous lupus, including classic discoid rash, hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
3. Oral ulcers OR nasal ulcers, in the absence of other causes
4. Nonscarring alopecia, in the absence of other causes
5. Synovitis involving ≥2 joints, characterized by swelling or effusion OR tenderness in and ≥30 min of morning stiffness
6. Serositis, including pleurisy for >1 d or pericarditis, in the absence of other causes
7. Renal disease, with a urine protein to creatinine ratio (or 24-h urine protein level) representing 500 mg protein/24 h OR red blood cell casts
8. Neurologic disease, including seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state, in the absence of other causes
9. Hemolytic anemia
10. Leukopenia (<4,000/mm^3) OR lymphopenia (<1,000/mm^3), in the absence of other known causes
11. Thrombocytopenia (<100,000/mm^3), in the absence of other known causes

Immunologic criteria:

1. ANA screen positive
2. Anti-dsDNA antibody positive (≥2-fold if tested by ELISA)
3. Anti-Sm (Sm nuclear antigen) antibody positive
4. Antiphospholipid antibody positive as determined by any of the following: positive test result for lupus anticoagulant, false-positive test result for rapid plasma reagin, medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM), positive test result for anti–*β*-2-glycoprotein I (IgA, IgG, or IgM)
5. Low complement test result, including C3, C4, or CH50
6. Direct Coombs test positive in the absence of hemolytic anemia

ANA=antinuclear antibody, dsDNA=double-stranded DNA, ELISA=enzyme-linked immunosorbent assay, IgA/G/M=immunoglobulin A/G/M, SLE=systemic lupus erythematosus, SLICC=Systemic Lupus International Collaborating Clinics.
Adapted with permission from Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. *2012;64(8):2677–2686. (7)*

examination, and laboratory and imaging studies; and for planning next steps.

Symptoms and Signs

These criteria particularly highlight the mucocutaneous manifestations that affect 75% of patients, including the well-known malar rash that affects the cheeks and the bridge of the nose. This rash can have "discoid" features, including erythematous scaly and/or atrophic involvement. Many patients first learn that they have skin photosensitivity when rashes appear or dramatically worsen with sun exposure or when they develop new sunburns or blisters out of proportion to their sun exposure. Skin changes can also result from the vasculitic nature of SLE, including RP with NFC changes, purpuric lesions unexplained by local injury or coagulopathy, and scarring lesions (especially on the digits) due to tissue infarction.

Oral mucosal lesions are common and can be painful or painless (Fig 3). Hard palate lesions are often colorful but painless, but most other lesions are painful. A painful pharyngitis and prominent cervical adenopathy may develop such that the patient might be thought to have an infectious disease such as streptococcal pharyngitis or infectious mononucleosis.

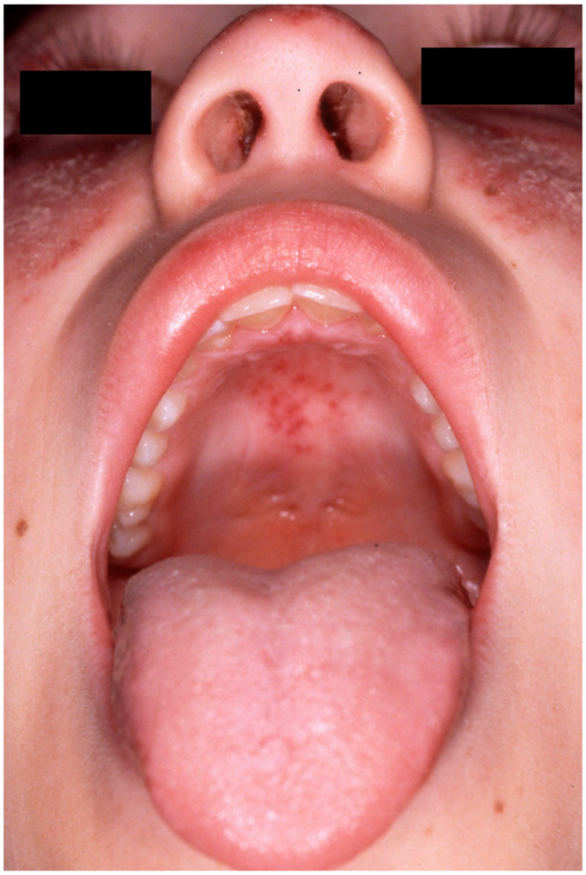
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Figure 3. Systemic lupus erythematosus with scaly malar rash and punctate erythematous rash on the hard palate.

Most children with SLE have arthritis, but the degree and pattern of involvement is highly variable. Joints of the upper or lower extremities may be involved in a way that suggests severe RA and can even be associated with the presence of RF, but it is not common to see early radiographic damage typical of RA.

Renal disease with active urinary sediment (hematuria, proteinuria, casts), and cytopenias are seen in most patients as well, and serositis and neurologic symptoms are slightly less common.

For the patient described in the case presentation, SLE could explain every one of the features of her problem list, not just RP and facial rash.

Diagnostic Approach

In addition to a complete history and physical examination, the findings on a complete blood cell count and urinalysis with microscopy can quickly provide evidence supportive of the possibility of SLE.

The antinuclear antibody (ANA) screening test takes longer and is nearly always positive. However, given the high background frequency for this result in normal children (25%), it is also a major cause of unnecessary anxiety when it is ordered for a patient with a low previous probability of SLE. A positive ANA screen in the right clinical context leads to follow-up testing for SLE-specific ANAs, including anti–double-stranded DNA antibodies (anti-dsDNA) and anti-Smith antibody, and testing for complement consumption (low C3 and C4). In contrast, a negative screening ANA result is strong evidence against the possibility of SLE.

There should also be consideration of screening for the extent of organ involvement, such as serum creatinine and albumin levels to help judge the severity of the renal injury suggested by an abnormal urinalysis result. Similarly, a quick look at the American College of Rheumatology and Systemic Lupus International Collaborating Clinics criteria with the patient in mind might suggest other relevant next steps, such as chest radiography when there have been symptoms or signs suggestive of pleural or pericardial disease.

Despite continuing efforts to refine classification criteria for SLE, the diagnosis can at times still be complicated because many other infections (Epstein-Barr virus, parvovirus B19, human immunodeficiency virus), autoimmune diseases (MCTD, Henoch-Schonlein purpura, antineutrophil cytoplasmic antibody–associated vasculitis), and even malignancies (leukemia, lymphoma) can present with symptoms or signs that mimic SLE. The classification criteria cannot be applied without consideration of these other possibilities, and input from an experienced rheumatologist or nephrologist should be sought to confirm the diagnosis.

Management

The successful long-term management of SLE depends on accurate characterization of the extent and severity of organ involvement, and then tailoring of therapy based on the individual's needs.

In terms of the immediate management of an outpatient in your clinic, symptomatic treatment for the arthritis or serositis can be provided with acetaminophen or with a nonsteroidal anti-inflammatory drug if there are no renal concerns. Common topical therapies for the mucosal or skin manifestations can also be recommended for temporary relief until a more definitive therapy plan is in place. Antihypertensive therapy may be needed for the patient with renal disease.

A more definitive plan for therapy usually gets started only after full characterization of the patient's condition, and the plan is tailored to be appropriate for the extent of involvement. This plan usually incorporates a combination of medications that have anti-inflammatory and/or immunosuppressive properties that reduce cytokine production, autoantibody production, complement activation, and infiltration of tissues by inflammatory cells.

Commonly used therapies include glucocorticoids, which provide fast-acting anti-inflammatory and immunosuppressive effects. With glucocorticoid therapy it is important to ensure adequate calcium and vitamin D intake and to consider needs for gastrointestinal protection. Nearly every patient with SLE will also receive hydroxychloroquine, which is anti-inflammatory and immune-stabilizing without causing immune suppression, and which can reduce the long-term need for glucocorticoids. Many patients require azathioprine, mycophenolate mofetil, or, in the most severe cases, cyclophosphamide, all of which suppress abnormal and normal immune function and can increase the risk of infections. Some of these therapies have significant implications regarding fertility or pregnancy, so counseling on these topics may be needed for both males and females. Newer therapies include belimumab and rituximab, biological molecules that target B lymphocytes. Reigning-in overactive B lymphocytes with these therapies is more commonly done for adult SLE; they are not Food and Drug Administration–approved therapies for childhood SLE.

The importance of the nonglucocorticoid therapies cannot be overstated, as it is now apparent that patients with SLE are living long and productive lives but having substantial morbidity attributable at least in part to their glucocorticoid treatment history, including accelerated atherosclerotic disease.

Prognosis and Follow-up

Although SLE can be immediately life-threatening, the most typical course is now that of a chronic disease with a persistent or relapsing course. With modern immunosuppressive and immunomodulatory therapies, a child is expected to have a long and productive life, but, unfortunately, the complexity and chronicity of the disease and its treatment can still result in substantial morbidity. It is important for there to be close collaboration between members of their primary clinic and the team specializing in SLE and the support of families, friends, and other community members to ensure the best quality of life and health.

DERMATOMYOSITIS

Definition

Dermatomyositis is an autoimmune disease featuring small vessel vasculopathy primarily affecting the skin and muscles, resulting in prominent rashes of the face and joints, and muscle weakness and fatigue that impair activities. It is sometimes complicated by significant involvement of other organ systems, especially the gastrointestinal and respiratory systems.

Epidemiology

Dermatomyositis affects both adults and children, and in children it primarily affects the school-aged group, although a substantial minority start earlier. Dermatomyositis is slightly more common in girls than in boys, but there are no major differences in its prevalence in children of different ancestry. The exact incidence and prevalence of childhood DM are not known, but its incidence is probably similar to that of SLE.

Pathogenesis and Presentation

As with other autoimmune disorders, the pathogenesis of DM seems to be multifactorial, with both genetic susceptibility and environmental triggers playing a role in its development. New cases are seen year-round, although seasonal variation of the rate of new cases has resulted in studies of infectious and environmental triggers. Certainly, the photosensitive nature of the disease can lead to flares or greater recognition during sunny times, but for most individuals, no triggering event will be apparent and no family history of another affected individual will be found.

Similar to other CTDs/CVDs, there are a variety of immunologic abnormalities evident in DM, including aberrant activity of the innate and adaptive immune systems. These abnormalities include activation of interferon-α pathways, autoantibody production, and inflammatory cellular infiltrates associated with a small vessel vasculopathy.

Symptoms and Signs

The symptoms and signs of DM reflect where the vasculopathy is most prominent, and the presentation and course for different patients can vary significantly. The clinical phenotype can sometimes be anticipated by the presence of particular "myositis-associated" or "myositis-specific" antibodies, but these associations are better characterized in adult populations than in childhood populations.

The typical patient with childhood DM presents with insidious onset of fatigue and fatigability with activities, often progressing to proximal muscle weakness that interferes with basic activities of daily living. Sometimes the onset can be acute, but it is not typically as abrupt as the myositis seen with viral illnesses such as influenza. The pattern of proximal muscle involvement is another feature that distinguishes it from acute viral myositis, which often causes distal injury such as painfully tender calf muscles.

The proximal weakness of DM leads to characteristic functional impacts, including difficulty getting on and off the floor, climbing stairs, climbing in and out of a vehicle, and even getting on and off the toilet independently. Upper extremity involvement leads to difficulty lifting objects with the arms, including difficulty getting items on and off elevated shelves, or even lifting the arms to do basic care activities such as combing hair. Neck muscle weakness can lead to difficulty with head control. In severe cases, pharyngeal muscle weakness leads to trouble with phonation and coordination of swallowing, and drinks can end up being misdirected out the nose or into the airway, resulting in aspiration. The child may even have trouble swallowing saliva without aspirating it. Respiratory symptoms can also develop due to profound respiratory muscle weakness or autoimmune lung disease of a variety of types.

On manual muscle testing, relatively symmetrical proximal muscle weakness may be detected. For a supine patient, trouble keeping the head off the table may be the most sensitive finding and indicates neck flexor weakness. Trouble lifting each leg indicates hip flexor weakness, and sit-ups test the hip flexors, abdominal muscles, and neck flexors. Trouble raising the arms while sitting upright tests the shoulder abductors. A nondeforming arthritis is not unusual, and both the arthritis and the myositis can contribute to contractures.

Before or after the onset of myositis, the patient will also have a dermatitis, which may have been overlooked or may have been prominent but not definitively recognized. In many cases, patients will report that they developed a sunburn, contact sensitivity, or unusual eczematous dermatitis that was unexpected in its onset, severity, or (lack of) improvement over time. On examination there is a typical distribution to the skin involvement. As with SLE, a prominent facial or malar dermatitis affecting the cheeks and the bridge of the nose is common, but there is also a distinctive involvement of the upper eyelids, with a violaceous color and sometimes edema (Fig 4A). This "heliotrope" rash is a pathognomonic feature of DM.

A scaly dermatitis with or without papules over the extensor surfaces of the finger metacarpophalangeal and proximal interphalangeal joints is commonplace, often with a mild streaky erythema between the joints (Fig 4B). The papules, known as Gottron papules, can seem like smooth, flat-topped warts and are nontender. A similarly scaly erythematous dermatitis can also occur over the extensor side of the elbows and knees and on the ankle malleoli. As with SLE, severe vascular injury can lead to infarcts of skin on the fingers or other areas, resulting in skin ulceration and calcium deposits (calcinosis) that can be confirmed with plain radiographs.

Striking changes to NFCs may be present, and because their condition is an indicator of the activity of microvascular disease, serial examination can be helpful for optimizing and monitoring medical therapy. The small vessel vasculopathy can also result in prominent gingival erythema evident on oral examination, but other oral lesions are uncommon.

Worrisome developments that may require emergency evaluation and possible hospitalization can include inability

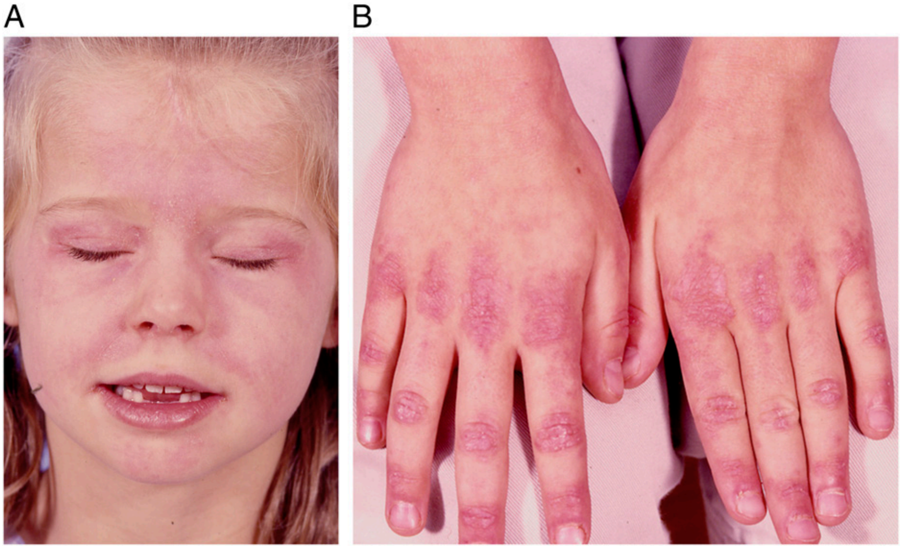

Figure 4. A. Dermatomyositis facial rash, with erythematous confluent scaly plaques over the forehead, upper eyelids, and cheeks. B. Dermatomyositis hand rash, with erythematous scaly plaques predominantly overlying the extensor surface of joints, associated with flat-topped shiny Gottron papules.

to transfer or ambulate safely, inability to swallow secretions or coughing that suggests aspiration, respiratory weakness that suggests a need for ventilatory support, or appendicitis-like abdominal pain that suggests intestinal perforation.

For the patient described in the case presentation, DM could explain every one of the features of her problem list, not just RP and facial rash.

Diagnostic Approach

The 1975 diagnostic criteria of Bohan and Peter (8) are still the primary diagnostic criteria in use. These criteria include characteristic skin changes and elevated skeletal muscle enzymes, as well as evidence on manual muscle testing of proximal muscle weakness, evidence of myopathy by electromyography, and evidence of characteristic muscle cell injury and inflammation on muscle biopsy.

The muscle enzymes that can become elevated from muscle cell injury include creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase. The pattern of elevation can vary over time, and the creatine kinase level (which is muscle specific) may not always be informative. Because the other enzymes have multiple sources, other tests (such as other liver function tests or a complete blood cell count) may need to be performed at the same time to aid interpretation.

Magnetic resonance imaging (MRI) of the proximal musculature, usually the thighs and pelvis, can also identify muscle injury and help guide site selection for a diagnostic muscle biopsy. An MRI and muscle biopsy may not seem needed when the diagnosis is obvious, but they can sometimes provide important diagnostic and prognostic information regarding the extent and severity of the inflammatory process and tissue damage and thereby impact decisions about initial therapy. Electromyography is performed much less commonly now since the introduction of MRI for evaluating DM.

Other common laboratory tests, such as basic hematology and chemistry panels, markers of inflammation, and markers of immune activation, are often normal or nonspecifically abnormal. Myositis antibodies, mentioned earlier, are abnormal in a minority of patients and are not yet universally obtained. Production of ANA is not a feature of DM.

Management

As with other complex multisystem diseases, it is important to characterize the extent of involvement to plan optimal therapy. A key step in the early evaluation and management is to assess the patient's functional limitations and safety in their home or school environment. Physical and occupational therapy evaluations can help in this regard, and there are standardized evaluation tools available to assist with tracking improvement over time. When there are severe manifestations, urgent multidisciplinary evaluation may be needed, including assessment of airway safety and pulmonary sufficiency, and intense medical therapy may need to be initiated before all results are available.

More commonly, medical therapy is started after the medical evaluation is complete. Glucocorticoids provide quick anti-inflammatory and immunosuppressive benefits but are almost always paired with additional anti-inflammatory and immunomodulatory therapies that help reduce glucocorticoid dependence and toxicity. The most commonly added anti-inflammatory medication is weekly low-dose methotrexate, given orally or subcutaneously. Similar to SLE, a variety of other corticosteroid-sparing medications can be used, including hydroxychloroquine, and potent immunosuppressives, such as calcineurin inhibitors (cyclosporine or tacrolimus), azathioprine, and mycophenolate mofetil. In urgent situations, intravenous immunoglobulin 2 g/kg is often used to gain quick control of the disease and can be repeated every 2 to 4 weeks. As with severe vascular diseases, there is sometimes a need for even more intensive therapies, including cyclophosphamide or rituximab.

Prognosis and Follow-up

Traditionally, children with DM are noted to follow 1 of 3 equally common patterns, including a group having a monophasic course with little or no residual effects, a second group having a relapsing course with highly variable results, and a third group with severe and chronic ulcerative disease. New insights learned from profiling based on myositis antibody and more detailed muscle pathology studies may allow for better subclassification of patients and tailoring of therapies for optimal care. The principles mentioned previously herein for SLE regarding setting expectations and encouraging teamwork and support are just as true for DM because most do not have a monophasic course, and DM's effect on all groups is significant.

SCLERODERMA

Definition

Scleroderma includes several inflammatory conditions that result in hardening of the skin due to fibrosis. They are commonly divided into 2 general categories. Those conditions known as a form of localized cutaneous scleroderma primarily involve the skin and sometimes adjacent deeper tissues. The conditions known as a form of systemic scleroderma (systemic sclerosis) may have a variety of additional manifestations, including life-threatening involvement of internal organs. Fortunately, most children with scleroderma have a form of localized cutaneous scleroderma rather than a systemic form.

Epidemiology

Scleroderma is estimated to affect approximately 300,000 individuals in the United States, most commonly affecting adults and more commonly affecting females.

Pathogenesis and Presentation

Although the etiology of scleroderma is unknown, as with other autoimmune disorders there is a role for genetic predisposition. Its pathogenesis features endothelial injury leading to loss of vascular integrity and subsequent edema, inflammation, and ultimately fibrosis. Vascular injury can also lead more directly to tissue damage, including necrosis of skin and other tissues. With systemic forms, the integrity and function of internal organs can be compromised and may result in life-threatening cardiopulmonary, renal, and visceral disease.

Symptoms and Signs

During the inflammatory phase there may be erythema or violaceous discoloration of skin, along with edema and pain. As with other conditions causing skin injury, there can be a postinflammatory hyperpigmentation or hypopigmentation, but often there are other notable findings that distinguish it from more common causes of skin injury, such as sun damage, trauma, or infection. In many cases, the fibrosis will manifest with discrete plastic-like firmness of the skin or subcutaneous tissue, and in some there will be a smooth, waxy hypertrophic appearance (Fig 5A). In other cases, there will be tissue injury, leading to localized atrophy of the skin and subcutaneous tissues, leaving the skin almost translucent and underlying structures (tendons, muscles) more easily discerned. The soft tissue injury may progress to involve deeper layers, leading the skin to become adherent to deeper tissues and even restricting the normal growth and development of cutaneous and musculoskeletal structures (Fig 5B). Restriction of the normal motion of joints may result. Many patients will have individual lesions of more than 1 type or lesions with mixed features, including a mixture of hyperpigmentation and hypopigmentation, atrophy, and hypertrophic fibrosis in linear and irregular plaque shapes.

For the patient described in the case presentation, systemic scleroderma would explain many features of her problem list, including RP, but not the scaly nature of her skin involvement.

Diagnostic Approach

Diagnosis of the skin disease is often made on clinical grounds but may also be confirmed by biopsy. There are no diagnostic laboratory tests for localized scleroderma. There can be evidence of immune activation with an elevated serum IgG or a nonspecifically positive ANA test, as well as nonspecific elevation of inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein. The distinction of localized forms from systemic forms is generally based on a thorough history and physical examination. Symptoms and signs that would suggest systemic disease include RP, ulcers of the digital tips, or other vascular events, as well as tenosynovitis, joint synovitis (arthritis), myositis, fasciitis, dysphagia or gastroesophageal reflux, or cardiorespiratory symptoms. As with SLE, a quick review of the consensus criteria can quickly facilitate recognition of important clues in the history or physical

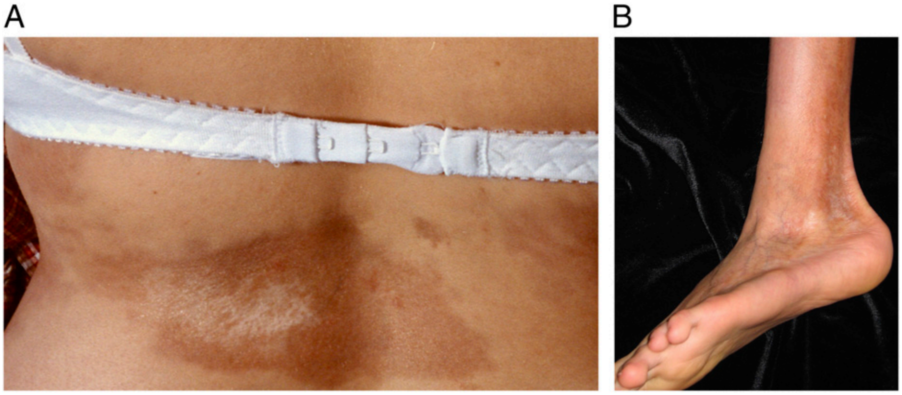

Figure 5. A. Localized cutaneous scleroderma (plaque morphea) on the back, with postinflammatory hyperpigmentation and hypopigmentation, waxy sclerosis, and atrophy. B. Localized cutaneous scleroderma (linear scleroderma) extending down the left lower leg, over the lateral malleolus, onto the dorsum of the foot, with marked postinflammatory hyperpigmentation and hypopigmentation, waxy sclerosis, and atrophy of subcutaneous tissues, resulting in vascular prominence.

examination that might facilitate assessment of whether a systemic illness seems likely (Table 3). In cases in which there may be extensive involvement of the skin or symptoms raising the question for systemic disease, testing for autoantibodies may be informative. With systemic forms of scleroderma, the ANA screen is often positive, with anticentromere or anti–scleroderma 70 specificities.

Management

Both local and systemic therapies are used for localized scleroderma. For limited disease that does not have significant cosmetic or functional implications, local therapy with immunomodulatory medications can be used, including topical or intralesional glucocorticoids, topical vitamin D analogues, or topical calcineurin inhibitors such as tacrolimus. For lesions causing significant cosmetic or functional implications, such as facial lesions or lesions affecting limb growth or function, systemic therapy is essential and rehabilitative services may be needed.

Options for systemic therapy continue to evolve and have significantly changed the management of localized cutaneous scleroderma during the past 25 years. Low-dose oral or subcutaneous methotrexate, as used for juvenile arthritis and DM, can help arrest progression and even allow remodeling and healing of lesions. Mycophenolate mofetil and other immunosuppressive therapies can be helpful for resistant disease, and there has been success reported with newer biological therapies currently approved for juvenile arthritis. For highly inflamed, symptomatic, or rapidly progressive disease, the addition of oral or intravenous glucocorticoids can help quickly reduce inflammation and provide time for methotrexate or other therapies to begin to work. The best methods for assessing residual active disease and, therefore, the timing of therapy withdrawal are still unknown and are an area of active research.

TABLE 3. PRES/ACR/EULAR Classification Criteria for Juvenile Systemic Sclerosis

A patient may be classified as having juvenile systemic sclerosis in the presence of the major criterion and 2 minor criteria.
Major criterion: Proximal skin sclerosis or induration
Minor criteria:
• Skin: sclerodactyly
• Vascular: Raynaud phenomenon, abnormal nail fold capillaries, digital tip ulcers
• Musculoskeletal: tendon rubs, arthritis, myositis
• Gastrointestinal: dysphagia, gastroesophageal reflux
• Pulmonary: pulmonary fibrosis, low diffusing capacity, pulmonary hypertension
• Cardiac: arrhythmias, failure
• Renal: renal crisis, new hypertension
• Neurologic: neuropathy, carpal tunnel
• Serologic: ANA or SSc-selective antibodies (anticentromere, Scl-70, and others)

ACR=American College of Rheumatology, ANA=antinuclear antibody, EULAR=European League against Rheumatism, PRES=Pediatric Rheumatology European Society.
Adapted with permission from Zulian F, Woo P, Athreya BH, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum. *2007;57(2):203–212. (9)*

TABLE 4. Distinctive Features of the Major Multisystem CVDs/CTDs

CONDITION	DISCERNING FEATURES
SLE	• Extensive multisystem (head-to-toe) involvement possible. Cytopenias, renal, and erythematous skin disease in most • ANA screen nearly always positive, and anti-dsDNA and anti-Smith are unique. Decreased C3 and C4 common
DM	• Erythematous scaly rash of face and joints, and proximal muscle weakness and elevated muscle enzymes • ANA screen negative
Scl	• Smooth, hardened skin with hyperpigmentation and hypopigmentation. Multisystem form is rare, with the rash unlike other SLE and DM • ANA screen often positive, and anti–Scl-70 or anticentromere specificities are unique
MCTD	• "Mixed" features of SLE, DM, Scl, and RA, but not renal disease • ANA screen nearly always positive, and anti-ribonucleoprotein antibody specificity always present and predominant

ANA=antinuclear antibody, CVD/CTD=collagen vascular disease/connective tissue disease, DM=dermatomyositis, dsDNA=double-stranded DNA, MCTD=mixed connective tissue disease, RA=rheumatoid arthritis, Scl= scleroderma, SLE=systemic lupus erythematosus.

Prognosis and Follow-up

At minimum, the hope is to arrest any progression of the disease, but often there will be fading and softening of fibrotic lesions and even reconstitution of subcutaneous tissue in atrophic areas. With optimal therapy there is the potential for normal growth and reconstitution of the soft tissue and deeper structures. Surgery to improve soft tissue or skeletal abnormalities is best performed only when the patient is in remission of medications because healing may otherwise be compromised.

CASE EXAMPLE PART 2: DIAGNOSTIC CONSIDERATION AND TESTING

Given the patient's rapidly growing problem list, the pediatrician screened for infectious, endocrine, oncologic, and rheumatic diseases that might explain her many problems. Testing for Epstein-Barr virus infection was negative. Electrolyte concentrations, creatinine level, and urinalysis results were normal, excluding any significant renal disease. Her thyrotropin level was normal. Blood counts were reassuring, with a white blood cell count of 4,200/μL (4.2×10^9/L), hemoglobin level of 12.8 g/dL (128 g/L), and platelet count of $286\times10^3/\mu$L (286×10^9/L). The uric acid level was low normal, and the lactate dehydrogenase level was only borderline elevated, suggestive of an inflammatory process rather than a malignancy. The C-reactive protein level was normal, but the erythrocyte sedimentation rate was elevated at 58 mm/h (reference range, ≤20 mm/h), consistent with active inflammation. The RF was strongly positive and the ANA screen was strongly positive.

Additional follow-up laboratory tests within a week showed elevation of the creatine kinase and aldolase levels and a hepatic panel with a borderline elevated aspartate aminotransferase level. There was mild lymphopenia (absolute lymphocyte count, 900/μL [0.9×10^9/L]). Specific ANA testing was negative for anti-dsDNA, but the anti–extractable nuclear antigen (anti-ENA) antibody panel was positive for anti-ribonucleoprotein antibody (anti-RNP) and negative for Smith antibody, Sjögren antibodies, and scleroderma antibodies.

AN APPROACH TO "RHEUMATOLOGY TESTS"

It is common practice for physicians to order "rheumatology tests" to screen for rheumatic diseases, but in children this is not an effective strategy. The best strategy is to establish a list of the most likely diagnoses and then use tests to increase or decrease the probability of alternative diagnoses and clarify the prognosis (Table 4).

In the case of the RF test, it is not specific to RA or to the childhood equivalent (RF-positive polyarticular JIA), which is a relatively infrequent arthritis in children. The RF test is often nonspecifically positive with infectious illnesses, including common infections as well as less common infections that can be associated with persistent problems, such as subacute bacterial endocarditis. It can also be positive in rheumatic diseases other than RA, such as SLE and MCTD.

Similarly, the ANA test is not specific and most commonly is not an indication of a health problem. In children, the background rate of positive results is approximately 25%, most often triggered by minor infectious illnesses. It is a commonly positive result in many subtypes of JIA, but its utility is not for diagnosis but rather for identifying the risk of developing a uveitis and establishing the frequency of screening ophthalmologic examinations. As mentioned, it is virtually always positive in SLE, and although it is an important confirmatory test for SLE, a negative result is what is often most informative because it makes this diagnosis highly unlikely. When there is a positive result, and SLE or a similar condition associated with specific ANA is suspected, then testing for specific ANAs can help clarify a diagnosis. The target antigens in the nucleus include native (double-stranded) DNA, or RNA-protein complexes. The physician can order a specific screening test for anti-dsDNA antibody and then screen for the other targets using an anti-ENA antibody panel. Antibodies against dsDNA are specific for lupus, as is the Smith antibody specificity in the anti-ENA antibody panel. Because these tests detect only a subset of specific ANAs, there is no reason to order these when the screening ANA result is negative.

Antibodies specific to scleroderma are commonly included in the anti-ENA antibody panel and are associated with systemic scleroderma. Antibodies associated with Sjögren syndrome are also part of the ENA panel but are not entirely specific to Sjögren and can be seen in SLE and other more limited forms of lupus, including neonatal lupus. Finally, anti-RNP antibody is a part of the ENA panel and occurs at lower values in SLE, but when it is present at high values and is the only positive specific antibody, anti-RNP suggests the diagnosis of MCTD, an interesting overlap condition that can have features of RA (including RF), SLE (but usually not renal disease), DM, and scleroderma. Mixed connective tissue disease should be considered in the list of possible diagnoses whenever a patient has RP or symptoms and signs suggestive of SLE, DM, RA, or scleroderma. Suspicion of MCTD should prompt ordering of a screening ANA and, if positive, then specific ANA testing.

CASE EXAMPLE PART 3: INTERPRETATION AND DIAGNOSIS

This patient had a symmetrical polyarthritis, which raised the possibility of RA. However, she had many extra-articular symptoms and signs, which suggested something more complex than RA. The patient also had muscle injury with elevated muscle enzyme levels and contractures, and the CVDs/CTDs that come to mind are DM, followed by SLE, and possibly scleroderma. The patient's rash was scaly, rather than smooth or fibrotic, so scleroderma was not a likely explanation. In contrast, a scaly malar rash is seen with both DM and SLE, and a scaly rash on joints of the hands is particularly suggestive of DM. When present, renal disease with active urinary sediment is suggestive of SLE, but this patient had no such difficulties. Otherwise, SLE is one of the few CVDs/CTDs that is multisystem and associated with RF and multiple other autoantibodies. Given that the patient had overlapping features of RA, DM, and SLE, it is not surprising that she turned out to actually have the overlap condition MCTD, as confirmed by a positive ANA test result that was uniquely associated with only the anti-RNP antibody specificity.

MANAGEMENT OF CVDs/CTDs

The CVDs/CTDs may cause both immediate and long-term problems, and the chance for and occurrence of such problems should not be underestimated but rather addressed head-on. The goals should be, in theory, to achieve disease remission and promote normal growth and development and a full and active life. More realistically, the goals are to make the patient healthier, minimizing any potential negative effects of therapy, and (as much as possible) to keep the child's condition and its treatment from interfering with a full and active life.

Many people are concerned about the therapies used for rheumatic diseases. It is important to emphasize that they are generally safe and effective when prescribed and monitored appropriately and that our knowledge about how to best help children with rheumatic diseases is improving all the time. Collaborative research networks are performing important work that continues to refine our understanding of the natural history of these conditions, the therapies, and how to optimize patient-centered care.

As for any child, but even more so for a child with a serious illness, a good working relationship with a primary care provider (and the clinic staff) for well-child care and acute illnesses is important. Prevention of infections through appropriate immunizations, and easy access for evaluation and management of new infectious illnesses, is especially important for these children given that these conditions and their treatment affect the child's ability to fight infections.

However, the primary care provider also plays an important role in making sure that the child's other general health needs are not negatively affected by his or her rheumatic disease and its treatment. They may have a better picture of the whole child and the family and the community in which they live through regular follow-up well-child care and may better know when and where special attention is needed. For example, the negative effects of glucocorticoid therapy include direct effects on the child (eg, visible effects on appearance, growth, or behavior, and less visible effects on bone, ocular, and cardiovascular health) and on the child's interactions with friends and family. Support from their families, medical professionals, and community organizations can have a hugely positive impact for patients newly diagnosed as having a chronic health condition and can promote their successful transition back to wellness.

Summary

- The conditions known as collagen vascular diseases (CVDs) or connective tissue diseases (CTDs) are individually uncommon, and their myriad symptoms and signs may appear asynchronously and highly variably.
- Timely and accurate recognition of the more common CVDs/CTDs can be facilitated through the familiar steps of collecting a comprehensive medical history, performing a complete physical examination, and creating a detailed list of past and current problems.
- The problem list for a child with a CVD/CTD may at first suggest a broad list of diagnostic possibilities. To sort out the possibility of a CVD/CTD, the published classification criteria can provide a quick reminder of their most distinctive features and help suggest appropriate next steps for further evaluation.
- Research evidence (1) and consensus suggest that if laboratory or imaging studies are needed for the evaluation of CVDs/CTDs, it is best to start with common tests that are easily obtained and quickly reported rather than with extensive and expensive "rheumatology tests."
- For concerning cases, such as children with rapidly growing multisystem problem lists, early discussion with a pediatric rheumatologist can help patients, parents, and providers feel assured that the plans for evaluation, treatment, and possible referral are on the mark.

References for this article are at http://pedsinreview.aappublications.org/content/39/10/501.

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1. You are evaluating a 12-year-old boy in your practice who has a history of several weeks of on-and-off fatigue and joint pain. The patient also has recent weight loss. He has had 2 episodes of nonstreptococcal pharyngitis. You suspect that he may have systemic lupus erythematosus (SLE), and you are considering ordering an antinuclear antibody (ANA) test. Which of the following is the most accurate characteristic of the ANA test and its role in establishing the diagnosis of SLE?
   - A. A negative ANA test result helps rule out SLE.
   - B. A positive ANA test result needs no follow-up testing.
   - C. Has a high positive predictive value.
   - D. Is highly specific.
   - E. Is positive in approximately 50% of the healthy population.
2. A 15-year-old adolescent girl, who is followed up in your clinic, has recently been diagnosed as having SLE with mild renal involvement based on clinical criteria and a positive ANA test result. She has no mucocutaneous features. Her complete blood cell count is normal except for mild anemia. In addition to nonsteroidal anti-inflammatory drugs for managing the fevers and arthritis, which of the following is the most appropriate initial treatment regimen in this patient?
   - A. Glucocorticoids.
   - B. Hydroxychloroquine.
   - C. Intravenous immunoglobulin.
   - D. Plasmapheresis.
   - E. Rituximab.
3. An 8-year-old boy is brought to the clinic with a 2-day history of heliotrope discoloration of the upper eyelids. In addition, the patient was noted 1 to 2 days earlier to have a symmetrical papular rash over the extensor surfaces of the joints, particularly the proximal interphalangeal, metacarpophalangeal, distal interphalangeal, elbow, and knee, consistent with Gottron papules associated with shiny, erythematous, scaly plaques. The patient has had multiple visits to the emergency department in the past 2 to 3 months for fevers, malaise, fatigue, and weight loss. Evaluations for infections and malignancy have been negative. Today, the parents noticed the discoloration of the upper eyelids and the rash and brought the child to the clinic for further investigation and management. You suspect one of the juvenile idiopathic inflammatory myopathies, particularly juvenile dermatomyositis. Which of the following clinical and/or laboratory findings is part of the Bohan and Peter criteria for the diagnosis of juvenile dermatomyositis in this patient?
   - A. Anemia of chronic disease.
   - B. Distal muscle weakness.
   - C. Elevated serum levels of skeletal muscle enzymes.
   - D. Family history of dermatomyositis in a first-degree relative.
   - E. Migratory muscle weakness.
4. The patient in the previous question underwent a full evaluation. Serum levels of skeletal muscle enzymes, including creatine kinase, aspartate aminotransferase, lactate dehydrogenase, and aldolase, were elevated. Physical examination was significant for weakness in his upper and lower extremities and difficulty combing his hair. Electromyographic and magnetic resonance imaging findings were consistent with juvenile dermatomyositis. Which of the following is the most appropriate next step in initial management in this patient?

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A. Cyclophosphamide.
B. Intravenous immunoglobulin.
C. Nonsteroidal anti-inflammatory drugs.
D. Prednisone.
E. Tacrolimus.

5. A 16-year-old girl developed multiple large areas of waxy hyperpigmentation and hypopigmentation on her legs and back. These skin changes have been progressing over the past 12 to 18 months. Periungal capillary changes are noted along with a progressively worsening perfusion and bluish discoloration of her fingers. Scleroderma is suspected. In addition to the findings described above, which of the following clinical findings is expected to be seen in the systemic form of this disease in this patient?

   A. Dysphagia.
   B. Generalized lymphadenopathy.
   C. Headaches.
   D. Hepatosplenomegaly.
   E. Visual changes.

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1 14-month-old Boy with Refusal to Bear Weight

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Struewing and Maul have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-month-old boy presents with fever; a swollen, erythematous left leg; and refusal to bear weight. Swelling and bruising were noted in the foot, ankle, and knee after being picked up from child care. He was febrile up to 100.9°F (38.3°C) at home. He has had cough and congestion for the past week with clear rhinorrhea. He was born at 36 weeks' gestation and has a history of chronic otitis media, which resolved with tympanostomy tube placement 2 months ago.

His vital signs are as follows: blood pressure, 105/53 mm Hg; heart rate, 152 beats/min; respiratory rate, 17 breath/min; and temperature, 98.2°F (36.8°C). The boy is sleepy but well-appearing and in no acute distress. He has normal range of motion of all joints, with minimal pain on manipulation of the left ankle. There is erythema over the lateral aspect of the ankle and the dorsum of the foot without fluctuance. He has no pain with passive motion of the hip or knee joints bilaterally. There is drainage from the left ear, suggesting acute otitis media.

Laboratory evaluation demonstrates a white blood cell (WBC) count of 16,200/μL (16.2×10^9/L), a C-reactive protein (CRP) level of 2.7 mg/L (25.71 nmol/L) (reference range, 0–10 mg/L [0–95 nmol/L]), and an erythrocyte sedimentation rate (ESR) of 27 mm/h. Radiographs of the tibia and fibula are normal. Left ankle arthrocentesis reveals bloody fluid with a WBC count of 8,463/μL (8.46×10^9/L). Magnetic resonance imaging of the left lower extremity demonstrated peroneal and anterior tibialis tenosynovitis and subtle myositis of surrounding musculature. He was taken to the operating room, where incision and drainage were performed. Aspirate fluid was collected, and further laboratory testing revealed the diagnosis.

DISCUSSION

The aspirate fluid was sent for routine cultures and Gram-stain, which were negative; a portion of the aspirate was inoculated in blood culture bottles. After incision and drainage by orthopedics, he was treated with vancomycin and ceftriaxone. The aerobic blood culture bottle grew gram-negative rods at 30 hours, and the patient was transitioned to ceftriaxone monotherapy. The boy quickly demonstrated decreased pain and increased range of motion, in addition to normalizing CRP. The gram-negative rod was identified as *Kingella kingae*.

The Pathogen

Kingella kingae is a member of the *Neisseriaceae* family. It is a facultative anaerobic gram-negative coccobacilli, typically presenting in pairs or short chains. (1) *Kingella* species are β-hemolytic and oxidase-positive. It is a nonmotile organism that grows on blood and chocolate agar but not on MacConkey agar. (2) *Kingella kingae* is becoming an increasingly common cause of bacteremia and osteoarticular infections in young children aged 6 to 36 months, and it is the most common etiology of joint infections in this age group, due in part to asymptomatic carriage in the oropharynx of children this age. (3) Spread of infection is thought to be due to a concomitant viral infection that damages epithelial cells already colonized by *Kingella*. This can result in a lower respiratory tract infection or invasion into the bloodstream, leading to infection of the skeletal system and other body parts. (2) In one series of 143 consecutive patients diagnosed as having *K kingae* infections, septic arthritis, osteomyelitis, and tenosynovitis accounted for 54.5% of diagnoses, occult bacteremia for 39.2%, lower respiratory tract infection for 3.5%, and ocular infections and bacterial endocarditis each for 1.4%. A review of the epidemiology of *Kingella* infections demonstrates that it most commonly affects the skeletal system, leading to septic arthritis, osteomyelitis, and, in a few reported cases, tenosynovitis. (3) *Kingella kingae* septic arthritis involves the large weightbearing knee, ankle, or hip joints in more than 80% of cases, and *K kingae* causes more than one-quarter of cases of spondylodiscitis in children younger than 5 years. Our patient was a regular attendee at child care, putting him at higher risk for *Kingella* colonization. He had *Kingella* tenosynovitis thought to be due to hematogenous myositis given magnetic resonance imaging findings and then subsequent extension into tendon sheaths.

Diagnosis

A thorough history and physical examination of the patient is crucial in helping to diagnose *K kingae* osteoarticular infections. It is becoming increasingly more common since its discovery, likely due to improvement in microbiologic evaluation of the specimen. *Kingella* is a fastidious organism and infrequently grows on routine culture. However, the probability of isolating *K kingae* is increased by inoculating the specimen in blood culture bottles. (2) In addition, the use of nucleic acid amplification aids in identifying *K kingae* as the etiologic organism.

Additional evaluation for children with this presentation typically includes inflammatory markers such as CRP and ESR, in addition to the complete blood cell count with differential count. Most children with *Kingella* infections, except those with endocarditis, are well-appearing to moderately ill. (3) They can be afebrile; inflammatory markers such as CRP level, ESR, and WBC count are frequently normal; and joint fluid with a WBC count less than 50,000/μL ($<50\times10^9$/L) more than 20% of the time fails to meet the laboratory criteria for septic arthritis. Because of the mild presentation of *K kingae* septic arthritis of the hip, this condition may be misdiagnosed as toxic synovitis, a benign inflammatory condition not requiring antibiotics for management. (3) Therefore, *K kingae* should be considered in children with inability to bear weight not responding to conservative management typically used in toxic synovitis. The history obtained by family, physical examination, and clinical suspicion helps to suggest the diagnosis of *Kingella*.

Management

With appropriate treatment, these children respond well to therapy and return to baseline activity levels. Children generally recover with no sequelae observed as long as the condition is recognized and treated in a timely manner and there is no endocardial involvement. (4) After initiation of appropriate antibiotic coverage, children typically return to weightbearing activity and normal playfulness in a couple of days. *Kingella* species are susceptible to β-lactam antibiotics in addition to macrolides, tetracyclines, and quinolones. (2) Outbreaks of *K kingae* infections are common in child care centers as children of 6 to 36 months are those who are typically colonized. Debate is still occurring regarding whether prophylactic antibiotics for outbreaks should be given. Rifampin has been shown to have good activity against *K kingae* infections, although further research is needed. (2)

Our patient was maintained on ceftriaxone until *K kingae* was identified and his musculoskeletal symptoms improved. The boy was discharged from the hospital on cephalexin to complete a total of 14 days of therapy. At the time of discharge, the patient was tolerating weightbearing activities and his normal state of playfulness.

Lessons for the Clinician

- *Kingella kingae* is a common pathogen identified in osteoarticular infections in children aged 6 to 36 months who attend child care, and it is the most common etiology of joint infections in this age group.
- A high index of suspicion is necessary to make the diagnosis of *K kingae* osteoarticular infections because of their often subtle clinical and laboratory presentation.

- Inoculating synovial fluid into aerobic blood culture bottles increases the likelihood of identifying *Kingella* musculoskeletal infections.
- Nucleic acid amplification assays, when available, can identify *K kingae* in less than 24 hours and decrease the number of bacteriologically unconfirmed pediatric skeletal infections.
- Skeletal infections due to *Kingella* have a fairly benign course with limited sequelae if appropriate treatment is initiated early after recognition of infection.

References for this article are at http://pedsinreview.aappublications.org/content/39/10/516.

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2

Headaches with Recurrent Rash and Mucosal Ulcerations

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PRESENTATION

An 18-year-old male from the Netherlands presents to the general pediatric clinic for follow-up from 2 visits to the emergency department (ED) with an approximate 1-week history of daily debilitating left-sided frontoparietotemporal headaches with associated intermittent photophobia, phonophobia, left-sided weakness, paresthesia, gait instability, bilateral hand tremors, and blurry vision. The headaches are exacerbated in intensity when supine and waking him from sleep. He denies associated nausea, vomiting, or abdominal pain. Onset occurred after his first presentation to the ED for recurrent oral aphthous stomatitis and erythema multiforme–like lesions. The headaches were poorly responsive to nonsteroidal anti-inflammatory drugs and acetaminophen; however, they would improve slightly with intravenous fluids, diphenhydramine, and prochlorperazine. Results of laboratory evaluation, including a urine drug screen and salicylate and alcohol levels, are normal. Results of noncontrast head computed tomography and magnetic resonance imaging are also reassuring.

His medical history was significant for depression, anxiety, polysubstance abuse, and herpes simplex virus-1 in addition to the recurrent oral aphthous stomatitis and erythema multiforme–like lesions. His aphthous stomatitis had been severe enough to require hospital admission 3 times in the past. During his first admission 4 years earlier, he had esophageal and genitourinary tract involvement in addition to the erythema multiforme–like lesions. Extensive evaluation by multiple specialists at that time did not reveal a unifying diagnosis. His second 2 admissions were in close proximity, within 12 months of his clinic presentation. He again had extensive aphthous stomatitis, erythema multiforme–like rash, and a small genital ulceration. A mouth lesion was biopsied and revealed a nonspecific autoimmune inflammatory process and no evidence of herpes infection.

His growth curve shows an approximate 5-kg weight loss over a 1-year period, with a BMI of 17.55 on the day of presentation. On physical examination he has a few scabbed, curvilinear papular lesions inferior to the bilateral periorbital regions. During the examination he develops a headache, becomes diaphoretic with bilateral hand tremor, and complains of photophobia and blurred vision. Review of previous records and expert consultation confirms the suspected clinical diagnosis.

DISCUSSION

The constellation of recurrent oral and genitourinary ulcerations, erythema multiforme–like lesions, and new-onset headaches with neurologic manifestations in the setting of otherwise unexplained weight loss suggested a clinical diagnosis of Behçet disease.

The Condition

Behçet disease is an autoimmune vasculitis that indiscriminately affects both arteries and veins of all sizes. (1) It is classically known to occur primarily along the "Silk Road," that is, the countries of Eastern Asia to the Mediterranean, Turkey being the most common (80–370 cases per 100,000 population). (2) Behçet disease is much less common in Northern European and North American populations. Specifically, countries of interest in this case include the Netherlands (prevalence of approximately 1 per 100,000) and the United States (0.33 per 100,000). (3) Young men are typically more severely affected than young women. Although the etiology of this disease is not yet fully understood, it is commonly associated with HLA-B51 (approximately 60% of affected patients) and can tend to cluster in families, although it does not have a known autosomal inheritance pattern. (4) It is postulated that multiple other genetic and environmental factors play a role in the manifestation of Behçet disease in an otherwise susceptible individual.

Behçet disease has the potential to affect any organ; however, it tends to primarily affect skin and mucous membranes. The classic triad is oral and genital ulcerations with uveitis, as originally described by Turkish dermatologist Dr Hulusi Behçet in 1937. (4) Approximately 97% of affected individuals have the classic oral ulceration, and 60% to 90% have recurrent genital ulcerations. Oral ulcerations can range from herpetiform (1–3 mm) to major (>10 mm). The genital ulcerations can involve any part of the genitourinary tract and commonly involve the scrotum in males and vulva in females. (1)

Dermatologic manifestations include papulonodular lesions, erythema nodosum–like lesions, acneiform rashes, pseudofolliculitis, pyoderma gangrenosum, and, less commonly, erythema multiforme–like rashes. (1) Individuals can exhibit a positive pathergy test result, which consists of an exaggerated, localized cutaneous reaction (such as papules, pustules, or ulceration) as a result of puncture from a sterile needle. This result is positive in only approximately 15% of Korean, 30% of British, and 60% of Turkish patients. This is also commonly seen in other neutrophilic dermatoses, such as Sweet syndrome or pyoderma gangrenosum, as well as other autoimmune inflammatory conditions, such as inflammatory bowel disease (IBD). (5) Our patient did not exhibit a positive reaction to pathergy testing in the office.

Behçet disease can also involve the gastrointestinal tract, strongly mimicking IBD and making it nearly indistinguishable. Biopsy of the patient's oral ulcerations from previous admissions showed an acute on chronic autoimmune process, composed predominantly of lymphocytic and neutrophilic infiltration, without evidence of granulomatous formation. Endoscopy and colonoscopy did not demonstrate evidence of acute colitis, although during 1 admission he did demonstrate esophageal ulcerations. Results of a fecal calprotectin test were negative.

Neurologic involvement can be a particularly serious complication, although it occurs in less than 10% of patients. (6) Individuals will typically present with either parenchymal or nonparenchymal involvement (ie, meningoencephalitis versus vascular complications, including cerebral venous thrombosis). Although headaches do not denote specific neurologic involvement as a direct result of the disease process itself, they are a common comorbidity and include predominantly tension headaches as well as migraine headaches. (6) As noted previously, results of magnetic resonance imaging performed in the ED were otherwise normal. Given the concern for potential vascular involvement due to the presence of headaches with other neurologic manifestations, magnetic resonance angiography/magnetic resonance venography was attempted; however, due to patient anxiety it was not able to be completed despite anxiolysis.

Along with neurologic involvement, a devastating feature of classic Behçet disease is ocular involvement, which can be particularly severe in males. It can manifest in forms of anterior/posterior uveitis, retinal vasculitis, scleritis, episcleritis, and thrombosis of retinal arteries and veins. Patients can often demonstrate ocular pain, visual disturbance/loss, and photophobia. Despite our patient's complaints of blurred vision and ocular pain, the results of an ophthalmologic evaluation were normal. (1)

Diagnostic Criteria

The 2 predominant clinical scoring systems for establishing a diagnosis of Behçet disease are the International Study Group (ISG) criteria from 1990 (Table 1) (7) and the International Criteria for Behçet's Disease (ICBD) from 2006 (Table 2). The ISG criteria are slightly more specific (96.0% vs 90.5%); however, the ICBD criteria are significantly more sensitive (94.8% vs 85.0%). (8)

Our patient met the criteria for both the ISG and ICBD scoring systems with recurrent oral ulcerations, recurrent genital ulcerations, and skin lesions consisting of both

TABLE 1. **ISG Criteria for the Diagnosis of Behçet Disease (7)**

Must have:
Recurrent oral ulceration—minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred ≥3 times in one 12-mo period
Plus ≥2 of the following:
Recurrent genital ulceration—aphthous or scarring observed by physician or patient
Eye lesions—anterior uveitis, posterior uveitis OR cells in vitreous on slit lamp examination OR retinal vasculitis observed by ophthalmologist
Skin lesions—erythema nodosum observed by physician or patient, pseudofolliculitis, papulopustular lesions OR acneiform nodules observed by physician in postadolescent patients not taking corticosteroids
Positive pathergy test—read by physician at 24–48 h

ISG=International Study Group.

erythema multiforme–like lesions and papulopustular lesions associated with exacerbations.

Differential Diagnosis

Given that Behçet disease can affect any organ, there are many other conditions that it mimics, and ultimately it is a diagnosis of exclusion. Systemic inflammatory conditions such as systemic lupus erythematosus, IBD, and celiac disease should be considered and ruled out. Adverse drug reactions should be taken into consideration. Sexually transmitted infections such as human immunodeficiency virus, herpes simplex virus-1/2, gonorrhea/chlamydia, and syphilis are potential confounders. Other conditions, such as cyclical neutropenia, vitamin deficiencies (B_{12} in particular), and Sweet syndrome, need to also be considered. In our patient, during previous hospital admissions, these conditions were taken into consideration, and extensive multidisciplinary evaluation effectively ruled these diagnoses out; however, the clinical diagnosis of Behçet disease was never given.

TABLE 2. **ICBD International Criteria for the Diagnosis of Behçet Disease (2006) (8)**

SIGNS/SYMPTOMS	POINTS
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurologic manifestations	1
Vascular manifestations	1
Positive pathergy test results[a]	1

A total score greater than 4 is positive. ICBD=International Criteria for Beçhet Disease.

[a] Pathergy test is not required in the primary scoring system, although, if conducted, an extra point may be assigned for a positive result.

Management

Immunosuppression is the mainstay of treatment. Acutely, this can be accomplished with both topical and systemic corticosteroids. Antibiotics (such as doxycycline) in a mouthwash form for oral mucosal ulcerations can reduce the bacterial load contributing to exacerbation and prolongation of healing. Pain control with topical or systemic analgesics is important during acute exacerbations, particularly when there is difficulty eating as a result of pain. Under the guidance of a rheumatologist, disease-modifying drugs such as azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus can be used to provide more extensive immunosuppression and better control of the disease. Consideration of adverse effects of such drugs and appropriate monitoring are key to proper management. (1)

Patient Course

After consultation with pediatric rheumatology, he was started on azathioprine 100 mg/d and was increased to 150 mg/d within a few weeks. His symptoms dramatically improved over 2 to 3 months, and he was symptom free and regained the previously lost weight by 6 months from the start of treatment. He had no further relapses within 18 months and was then lost to follow-up due to relocation.

Lessons for the Clinician

- The clinician should be able to recognize the classic clinical pattern and be suspicious for Behçet disease, particularly the hallmark presentation of recurrent oral and genital aphthosis with other systemic manifestations.
- The clinician should recognize the differential diagnosis for Behçet disease and consider the diagnosis to be one of exclusion, ruling out more common etiologies such as sexually transmitted diseases, systemic inflammatory conditions (eg, inflammatory bowel disease, systemic

lupus erythematosus), Sweet syndrome, celiac disease, cyclical neutropenia, and vitamin deficiencies.
- The clinician should recognize the need for advanced imaging in the setting of neurologic signs/symptoms with a clinical suspicion of Behçet disease. In addition to magnetic resonance imaging, magnetic resonance angiography/magnetic resonance venography should be performed to help determine vascular involvement versus parenchymal involvement.
- The clinician should recognize the need for multidisciplinary evaluation of individuals suspected of having Behçet disease. This will include referrals to rheumatology and ophthalmology, and may include gastroenterology, neurology, urology, and/or dermatology based on symptoms.

NOTE. The views expressed in this article are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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3 A 10-year-old Boy with Saber Shins

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AUTHOR DISCLOSURE Drs Fabie and Misra have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 10-year-old boy is seen for evaluation of short stature and tibial deformity. His medical history is notable for term birth with the following birth parameters: birth weight, 2,460 g (<10th percentile); length, 19.1 in (48.5 cm) (50th–75th percentile); and head circumference, 13 in (33 cm) (25th–50th percentile). His medical history is significant for at least 5 long bone fractures with low-impact trauma as a toddler (Table 1). On physical examination he is thin-appearing, with height at the 4th percentile and weight at the 23rd percentile. Striking anterior bowing of his tibiae (Fig 1) and bowing and decreased forearm supination are observed. There is absence of dental anomalies and scleral discoloration. A skeletal survey demonstrates Wormian bones, diffuse osteopenia, multiple areas of periosteal and cortical thickening, and calcification of the interosseous membrane between the radius and ulna (Fig 2). Specialized testing reveals the diagnosis.

DISCUSSION

Because of the significant tibial bowing, prenatal maternal rapid plasma reagin was reviewed and was noted to be nonreactive. Initial analysis of type I procollagen produced by cultured dermal fibroblasts did not find alterations in the quantity or structure of the type I procollagen molecules made. Sequencing and deletion/duplication analysis of the *COL1A1* and *COL1A2* genes did not reveal any pathogenic changes. Laboratory studies demonstrated an insufficient 25-hydroxyvitamin D level (25 ng/mL [62 nmol/L]; reference range, >30 ng/mL [>75 nmol/L]), an elevated alkaline phosphatase level (491 μ/L [8.2 μkat/L]; reference range, 100–325 U/L [1.7–5.4 μkat/L]), normal calcium and phosphorous levels, and elevated spot urine N-terminal telopeptide levels (NTx; 574 nM BCE/mM Cr; reference range, 152–505 nM BCE/mM Cr). Bone mineral density by dual-energy radiograph absorptiometry showed a total-body *Z* score of –3.4, indicating bone mineral density below the reference range. Molecular genetic testing identified a pathogenic mutation in the *IFITM5* gene, confirming a diagnosis of osteogenesis imperfecta (OI) with calcification in interosseous membranes (OI type V).

TABLE 1. **Summary of the Patient's Trauma-Related Injury**

AGE (MO)	MECHANISM OF INJURY	TYPE OF INJURY
9	Fell off bed	Hairline fracture, distal metaphysis, right tibia
12	Slipped while holding furniture	Fracture, left tibia
26	Fell while playing	Fracture, right radius and ulna
39	Fell off bed	Nondisplaced distal fracture, left fibula
39	Fell from mother's arms	Nondisplaced distal fracture, left ulna

THE CONDITION

Osteogenesis imperfecta is a group of genetic connective tissue disorders characterized by bone fragility and bone deformity. Traditionally classified into 4 types—OI types I to IV—the identification of new causative genes and expansion of clinical features have led to the addition of new types. Table 2 summarizes the common OI types. Clinically, OI is one of the common disorders with variable expressivity. Each type may present with isolated findings of each or a combination of these clinical features: recurrent fractures, short stature, skeletal abnormalities such as bowing of long bones, and radiographic features of skeletal dysplasia (Wormian bones, diffuse osteopenia, cortical abnormalities). Laboratory markers of bone turnover (urine NTx, serum alkaline phosphatase) are also elevated. There may be other clinical features, such as blue sclerae, hearing loss, dental abnormalities, and joint laxity, but the presence of these highly depends on the type of OI.

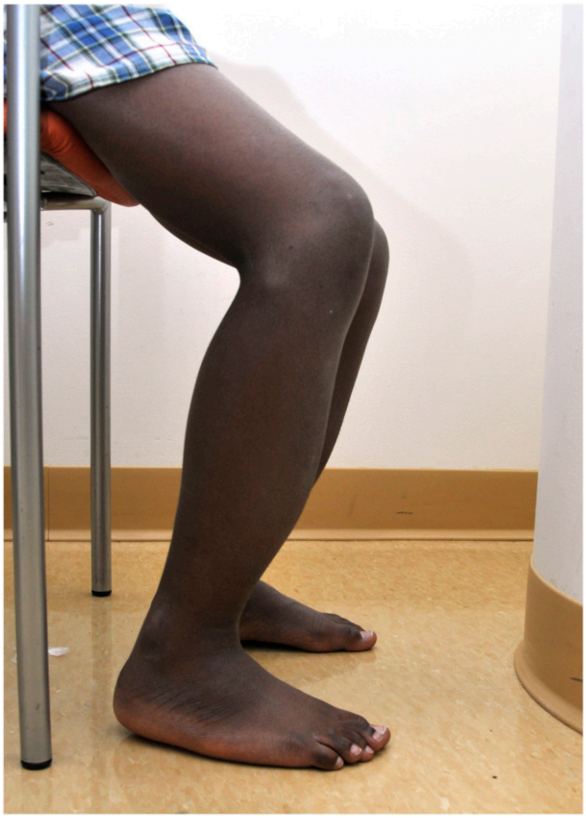

Figure 1. Anterior bowing of the tibiae (saber shins).

Similar to its clinical presentation, OI is also a genetically heterogenous disorder. Mutations in the *COL1A1* and *COL1A2* genes account for approximately 85% to 90% of known OI cases. However, during the past decade, genomic technologies have helped revolutionize our understanding of OI, identifying 15 additional genes, to date, that are associated with the disorder.

Osteogenesis imperfecta type V is an autosomal dominant form caused by mutations in the gene *IFITM5*. Patients with this type of OI have moderate or severe bone fragility with progressive calcification of the interosseous membrane. (2) This progressive calcification of the interosseous membrane is unique to this type and may often lead to decreased range of pronation/supination of the forearm and eventual radial head dislocation. Blue sclerae and dentinogenesis imperfecta are typically absent. Wormian bones or accessory skull bones within sutures are nonspecific findings in OI and have been described in OI type V. (3)

DIFFERENTIAL DIAGNOSIS

Our patient presented primarily with anterior bowing of the tibia or "saber shin" deformity. This deformity has been traditionally associated with the treponematoses, particularly late congenital syphilis. However, in developed countries, congenital syphilis is now rarely encountered. Thus, the incidence of this once common infectious disease is now similar to that of rare genetic disorders. As a result, skeletal dysplasias, including OI, various osteochondrodysplasias, and rickets have become a primary

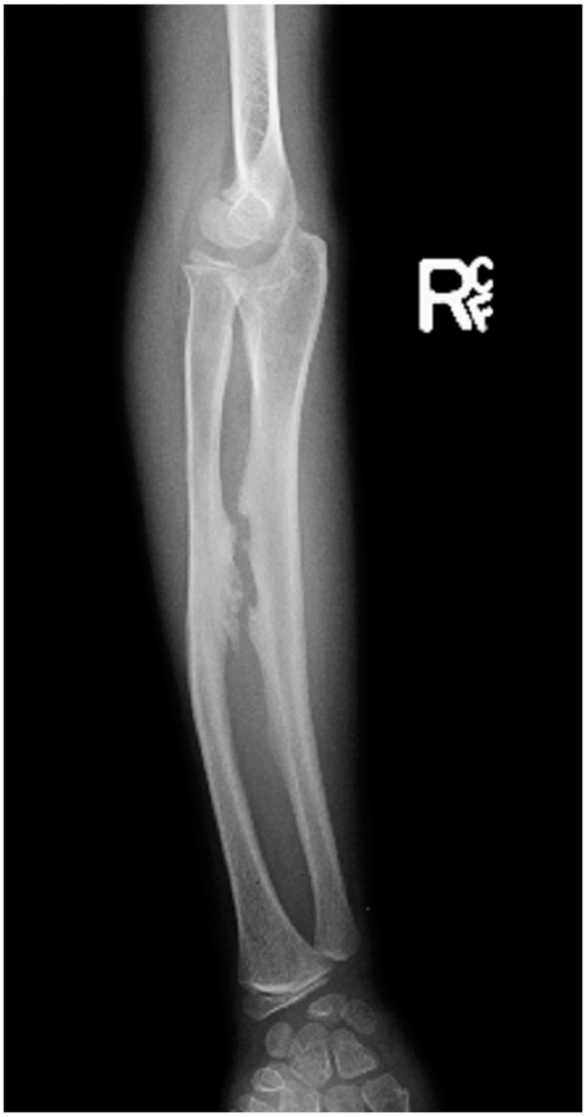

Figure 2. Cortical thickening, bony excrescence, and calcification of the interosseous membrane between the right radius and ulna.

consideration in the differential diagnosis of anterior tibial bowing in children. These conditions may be suspected and differentiated based on classic clinical and radiographic findings. Neurofibromatosis type 1 can present with limb deformities but usually is accompanied by café-au-lait spots.

Whereas rickets may also present with similar features of short stature, progressive long bone deformities, diffuse osteopenia, and fractures, the clinical markers of bone turnover and the radiographic features differ. The degree of vitamin D deficiency would usually be more severe and chronic before bony changes are identified. Renal function and/or liver function may be abnormal if the etiology of rickets is due to chronic liver disease or renal tubular acidosis. Radiographic features of rickets, such as flaring of the anterior aspects of the ribs (rachitic rosary) and widening or splaying of the metaphysis, are not common in OI, and interosseous calcification is usually not seen in rickets. In our case, radiography demonstrated the classic features of cortical thickening and bony excrescence of the interosseous margin of the ulna found in OI type V.

DIAGNOSIS

The diagnosis of OI requires an index of suspicion based on classic clinical and historical features, while accounting for unusual elements of the presentation. Laboratory markers of bone turnover (urine NTx, serum alkaline phosphatase), which are elevated in OI, are also used. Identification of radiographic features will also help guide further molecular genetic testing.

Until the advent of gene sequencing–based methods, the primary test to establish a diagnosis was the electrophoretic analysis of type I procollagen produced by cultured dermal fibroblasts to detect the quantity and structure of type I procollagen. Although this testing could distinguish patients with OI type I, it provided little insight into other forms of OI. Thus, the current first-line strategy to confirm a diagnosis of OI relies on sequence analysis of *COL1A1*, *COL1A2,* and other genes known to cause rarer forms of OI. If the clinical features suggest a specific form of OI, the specific gene testing to confirm the most likely diagnosis is performed. For nonspecific or atypical presentations, all genes can be sequenced concurrently.

MANAGEMENT

The goal of therapy for patients with OI is to maximize their quality of life by decreasing pain and disability while improving mobility and function. Like other forms of OI, the mainstay of treatment for individuals with OI type V include physiotherapy, rehabilitation, and, if necessary, orthopedic intervention. Health supervision considerations for OI were outlined by Starr et al in 2010. (4)

Children with OI type V, as in some forms of OI, may also benefit from cyclic intravenous bisphosphonates to improve bone density and reduce symptoms of osteoporosis. Effect on functional parameters in children, such as improved energy, decreased bone pain, and increased ambulation, are also seen with treatment. Treatment is

TABLE 2. OI Nomenclature with Causative Genes and Clinical Presentation (1)(2)

OI SYNDROME NAME	TYPE	GENES	FEATURES
Nondeforming with blue sclerae	I	AD: *COL1A1, COL1A2*	Bone fragility with fractures, blue sclerae, conductive hearing loss
Perinatally lethal	II	AD: *COL1A1, COL1A2* AR: *CRTAP, LEPRE1, PPIB*	Multiple, severe fractures involving ribs, long bones leading to deformed and crumpled bones; deficiency of ossification of facial and skull bones
Progressively deforming	III	AD: *COL1A1, COL1A2* AR: *BMP1, CRTAP, FKBP10, LEPRE1, PLOD2, PPIB, SERPINF1, SERPINH1, TMEM38B, WNT1, CREB3L1*	Bone fragility with multiple fractures, short stature, progressive kyphoscoliosis, angulation deformities of long bones, "popcorn" appearance of metaphyses, platyspondyly
Common variable OI with normal sclerae	IV	AD: *COL1A1, COL1A2, WNT1* AR: *CRTAP, PPIB, SP7* XL: *PLS3*	Fractures, osteoporosis, variable degree of long bone deformity; high risk for basilar impression
OI with calcification in interosseous membranes	V	AD: *IFITM5*	Calcification of forearm interosseous membrane, radial head dislocation, hyperplastic callus formation

AD=autosomal dominant, AR=autosomal recessive, OI=osteogenesis imperfecta; XL=X-linked.

given intravenously, and complications that have been described include flulike symptoms ("acute phase reactions") with the first infusion and transient hypocalcemia. (1)(5)

Lessons for the Clinician

- Anterior bowing of the tibia may be seen in an extensive number of diseases from infectious etiologies to genetic syndromes.
- Osteogenesis imperfecta (OI) is highly variable in its clinical presentation, and molecular testing via sequencing of genes associated with OI is necessary to obtain a definite diagnosis.
- Intravenous bisphosphonate treatment in OI has been shown to improve bone density and decrease disability in children with OI.

References for this article are at http://pedsinreview.aappublications.org/content/39/10/523.

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Index of Suspicion

4 Unexplained Fever in a 5-month-old Boy

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AUTHOR DISCLOSURE Drs Auriemma and Haberman have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 5-month-old previously healthy African American boy presents to the emergency department (ED) with an 8-day history of high-spiking daily fevers between 102°F and 104°F (38.9°C–40.0°C). On his second day of fever, he was diagnosed as having an acute suppurative otitis media by his primary care physician and was started on amoxicillin. Daily fevers continued despite adequate antibiotic compliance. Other than fever his only reported symptom is fussiness. Specifically, he has no cough, congestion, rash, vomiting, diarrhea, or change in appetite. In the ED his temperature is 103.1°F (39.5°C); heart rate, 175 beats/min; respiratory rate, 26 breaths/min; blood pressure, 98/64 mm Hg; and oxygen saturation, 98% on room air. He is ill-appearing and fussy but consolable. Subtle injection of the bulbar conjunctiva is present bilaterally without exudate. His heart rate is tachycardic, with regular rhythm and no murmur. His abdomen is soft and without organomegaly. His extremities are warm, well-perfused, and without edema. His lungs are clear to auscultation with normal respiratory effort. He has no rash or lymphadenopathy. The remainder of his examination findings are normal.

Laboratory values obtained in the ED reveal anemia with a hemoglobin level of 7.6 g/dL (76 g/L) and thrombocytosis with a platelet count of $486\times10^3/\mu L$ ($486\times10^9/L$). His white blood cell (WBC) count is normal, C-reactive protein level is elevated at 102 mg/L (971 nmol/L), and erythrocyte sedimentation rate (ESR) is elevated at 61 mm/h. Results of an electrolyte panel including liver enzymes, albumin, and renal function are normal. A urinalysis performed by bladder catheterization shows no sign of infection. Results of a respiratory viral panel obtained as part of an unexplained fever evaluation are negative. Chest radiography shows a normal cardiac silhouette and absence of pulmonary disease.

DISCUSSION

A key point before proceeding with a broad evaluation for fever of unknown origin is whether this patient needs to be promptly evaluated for Kawasaki disease (KD).

The classic diagnosis of KD requires at least 5 days of fever and at least 4 of the 5 principal features: extremity changes (erythema and/or induration of the palms or soles, periungual desquamation), polymorphous rash, bilateral nonexudative bulbar conjunctivitis that is often limbus-sparing, cervical lymphadenopathy greater than 1.5 cm, and changes of the lips, tongue, and/or oral mucosa (red/cracking lips, oropharyngeal erythema, strawberry tongue). (1) Note that these features are not always present at the same time; therefore, historical report both by caregivers and previous health-care providers is meaningful. A significant portion of patients (15%–36%) (2) do not present with full classic criteria yet are at risk for complications of KD. An algorithm endorsed by the American Academy of Pediatrics and the American Heart Association for incomplete KD provides guidance for patients who fulfill the fever requirement but have only 2 or 3 principal features. For these patients an ESR and C-reactive protein should be obtained, and if systemic inflammation is present further supplemental lab criteria should be pursued. This includes evaluating for age-based anemia, hypoalbuminemia (albumin level ≤3 g/dL [≤30 g/L]), elevated alanine aminotransferase level, thrombocytosis (platelet count $\geq 450 \times 10^3/\mu L$ [$\geq 450 \times 10^9/L$] after 7 days of fever), leukocytosis (WBC count $\geq 15{,}000/\mu L$ [$\geq 15 \times 10^9/L$]), and sterile pyuria (≥10 WBCs per high-power field). (1)

Our patient has only 1 clinical feature (bilateral nonexudative conjunctivitis) and does not meet the classic criteria, and neither does he fall under the incomplete algorithm as described previously herein. However, it is important to note that there is an exception on the incomplete algorithm for infants 6 months of age or younger. In this age group, if an infant has fever for 7 or more days without a source, laboratory testing to evaluate for KD should be performed. If systemic inflammation is present, an echocardiogram is recommended even if no clinical criteria are present and regardless of the results of supplemental laboratory criteria. (1)

Patient Course

An echocardiogram performed on day 9 of fever revealed a moderate aneurysm of the proximal right coronary artery of 0.37 mm (*Z* score +7), diffuse ectasia of the proximal left anterior descending artery of 0.30 mm (*Z* score +6.6), and a prominent circumflex artery. The patient was given a 2-g/kg single infusion of intravenous immunoglobulin (IVIg) and was started on high-dose aspirin (100 mg/kg per day). He continued to have fever 36 hours after completion of IVIg and was given a second infusion of IVIg on day 12. His fevers returned approximately 48 hours after completion of the infusion. He was then given 30 mg/kg of IV methylprednisolone on day 16. A follow-up echocardiogram was obtained at this time that showed that the proximal right coronary artery aneurysm increased by 0.08 mm, the ectasia of the proximal left anterior descending artery remained unchanged, and the circumflex artery became moderately enlarged. A new small (0.34-cm) aneurysm of the left main coronary artery also developed. At this time, a dose of infliximab (5 mg/kg) was given in addition to his 2-day corticosteroid course. He had no further fevers after a single dose of infliximab. Repeated echocardiograms 2 and 5 days after infliximab therapy showed stabilization of the size of his cardiac aneurysms. Computed tomography angiography of his chest, abdomen, and pelvis was negative for other signs of vasculitis or aneurysms. After more than 96 hours of being afebrile, he developed a new fever several days after receiving infliximab. Because infliximab can increase susceptibility to bacterial infections, further evaluation for possible infection was pursued. His fever was attributed to a *Klebsiella* urinary tract infection (>100,000 colony-forming units). He was treated with ceftriaxone, and fevers promptly resolved. He was discharged from the hospital on low-dose aspirin.

One month after discharge all of his coronary arteries returned to normal size. Owing to the severity of his initial presentation, he remained on aspirin therapy for 12 months.

The Condition

Young infants with KD are more likely to present with few or no classic features (3) and are at increased risk for coronary artery aneurysms. (4) Even infants diagnosed and treated within the first 10 days of fever have an increased incidence of coronary artery changes at the time of first echocardiogram, with some studies reporting rates as high as 43%. (4)(5) Of those with normal coronaries at the time of the first echocardiogram, more than 25% developed coronary changes even after appropriate treatment. (5) Therefore, high clinical suspicion in this age group is crucial to minimize morbidity.

Management

Typical treatment of KD involves high-dose aspirin plus IVIg as first-line treatment, with a second dose of IVIg given if the patient continues to have fever more than 36 hours after the initial dose. If fever persists after the second dose, potential therapies include corticosteroids, infliximab, other immunomodulators, and plasma exchange. (6) Disease that is IVIg resistant is associated with higher rates of coronary artery aneurysms. (7) Multiple predictive models have been developed to identify potentially resistant patients before treatment failure. Scoring systems that have proved useful in Japanese populations have not been shown to be as sensitive in other populations. (8) However, with multiple studies in recent years showing high safety and efficacy of infliximab for IVIg-resistant disease, (9)(10)(11)(12) some centers are adding infliximab early in the disease course for known high-risk populations, such as young infants and patients who already have coronary artery dilation or aneurysm at the time of diagnosis. (5)

Lessons for the Clinician

- Evaluate for Kawasaki disease (KD) in all infants younger than 6 months with fever for more than 7 days without other explanation, regardless of the absence of clinical criteria.
- Infants younger than 6 months with KD frequently present with coronary artery changes or develop changes despite appropriate treatment.
- Infliximab is a safe and effective second-line treatment for intravenous immunoglobulin–resistant KD and is emerging as a potential adjuvant therapy for high-risk patients such as infants and those who present with coronary artery changes.

References for this article are at http://pedsinreview.aappublications.org/content/39/10/527.

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Effects of Homelessness on Children

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AUTHOR DISCLOSURE Drs Dwomoh and Dinolfo have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

More than 4 walls and a roof, the word "home" evokes many emotions and images. For children, home should be a place of safety and security, a place of love and nurturance, where individuality, self-esteem, and confidence grow. Home is the place where children evolve into their best selves.

Although the data associated with homelessness are complicated by the various involved federal agencies using different definitions, the rate of homelessness among children in the United States must raise universal concern among pediatricians and other stakeholders in the welfare of our children and pose a call to action. A homeless person is reasonably defined as anyone who does not have stable housing and who, therefore, is living on the streets, in a shelter, in a mission or a single-room occupancy unit, or in an abandoned building or vehicle. In 2017, an average of 550,000 people in the United States, of whom 21% were children, were homeless on any given night according to the Department of Housing and Urban Development. By one estimate, 2.5 million American children, half of them younger than 6 years, experience homelessness each year. Among them are "runaways," youths who left home either of their own volition or because their parents pushed them to leave. For many, irreconcilable conflicts or loss of contact with their families makes it impossible for them to return home. Many are victims of abuse or have spent time in foster care. Although the challenges of identifying these young people often lead to them being lost from the count of the homeless population, some estimates suggest that approximately 500,000 youth experience at least 1 week of undomiciled existence each year.

Children are homeless in every state, in every city, and in every county in the United States. We may not see them on our streets, but families with children are hidden away from sight in shelters, abandoned buildings, crowded in with family members or friends, living in their cars. Families that have experienced long periods without permanent housing face persistent instability, measured by frequent moves and continued flux because of economic hardship, unemployment, physical or mental health problems, addiction disorders, domestic violence, or childhood abuse … a vicious cycle.

The causes of homelessness for families are myriad, with the most frequently cited reasons including a lack of affordable housing, unemployment, poverty, domestic violence, and the challenges of single parenting. Although childhood poverty rates in America have declined, approximately 25 million children live below federal standards for adequate income levels, with the highest rates found in single-parent homes led by Hispanic and black women: the rate of poverty among single-mother families is 5 times that of families with 2 parents. In addition, disasters such as hurricanes, tornadoes, flooding, and fires all lead to unexpected short-term homelessness that may persist, especially in families already living in tenuous economic conditions.

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Hidden in Plain Sight: Homeless Students in America's Public Schools. Ingram ES, Bridgeland M, Reed B, Atwell M. July 2016. Available at: http://www.americaspromise.org/report/hidden-plain-sight. Accessed July 30, 2018

The Mental and Physical Health of Homeless Youth: A Literature Review. Edidin JP, Ganim Z, Hunter SJ, Karnuk NS. *Child Psychiatry Hum Dev.* 2012;43(3):354–375

For unaccompanied youth, the chief factors underlying their homelessness include personal or family mental illness, substance abuse, and lack of affordable housing. Recently, more youth are made homeless when their families learn they belong to the LGBTQ community and disenfranchise them.

Children without a stable home are at risk for a host of adverse outcomes. Poverty, hunger, exposure to parental depression, or domestic violence may precede the loss of their home and contribute to the adverse outcomes seen in these displaced children. Homeless children are more likely to experience physical and behavioral health problems with less access to medical, mental health, and dental care.

More than a quarter of homeless children report having witnessed violence, and more than half have evidence of anxiety and depression. It is not uncommon for homeless children to be separated from their parents, some being placed in foster care and others left by their parents with relatives or friends. This separation may contribute to anxiety, depression, anger, conduct disorders, posttraumatic stress disorder, and poor school performance.

The ability of homeless children to meet their potential as individuals and contributing members of society is severely compromised. Inadequate shelter, insecurity, lack of services, and barriers to whatever services may be available all exacerbate the hunger and poor nutrition; the psychological, behavioral, and medical problems; and the educational failings and developmental delays that plague homeless children.

Environmental factors contribute to poor health outcomes. With the inadequacy of temporary shelter, homeless children are at increased risk for asthma, lead poisoning, and recurrent infections that can be particularly disabling in the context of poor nutrition, which also plays a role in lagging growth, poor dental hygiene, and educational and developmental delays. Despite the burden of their needs, homeless children generally lack access to consistent healthcare, and other resources and services vary from state to state and community to community: health insurance, the Supplemental Nutrition Assistance Program (SNAP), the Supplemental Nutrition Program for Women, Infants, and Children (WIC), and housing vouchers are not equally available in all parts of the United States. Compared with children living in stable homes, homeless children are more than twice as likely to have health problems and 3 times more likely to experience severe medical problems. They are more likely to miss meals and to worry about when they next will eat. Their diets, low in nutritional quality and high in fat content, contribute to high rates of malnutrition, poor linear growth, and obesity.

The unrelenting stresses experienced by the parents of homeless children, most of whom are women on their own, often lead to depression, anxiety, posttraumatic stress disorder, and other disorders that result in ineffective parenting. The effect on the children, particularly young children, can be permanently damaging, leading to changes in brain architecture that affect cognitive skills and learning, as well as emotional self-regulation and social relationships.

Homeless children are more likely than their peers to experience abuse, witness and experience violence, and have emotional trauma. Their transience, with frequent moves that interfere with stable schooling, affects educational achievement, leading to significantly lower rates of literacy. Compared with low-income children in secure homes, homeless children perform more poorly on mathematics and reading achievement tests. Both low self-esteem and the lack of constancy that comes with frequent dislocations contribute to the unlikelihood of making lasting friendships and appropriate social adjustment as the child grows.

Children without a stable home are more than twice as likely as their peers to repeat a school grade, have high rates of absenteeism, be cited for behavioral issues, drop out of school, or be expelled or suspended. Of homeless adolescents who receive crisis services while in a homeless shelter, only approximately one-third attain a high school diploma or general equivalency diploma by 18 years of age.

Homeless youth who are on their own, having run away from home or having been left unaccompanied, differ from homeless children in families. They are more often exposed to violence and exploitation and are more likely to engage in high-risk sexual behaviors and drug use and to suffer from mood and anxiety disorders. Homeless adolescent girls are more likely to become pregnant than girls who reside with their families in stable homes.

Given the wide-ranging negative effects of homelessness on a child's overall health and potential, pediatricians should be prepared to help families mitigate these effects as much as possible. By being aware and integrating that awareness into their practices, by partnering with community-based services, and by actively advocating for families facing homelessness, pediatricians can help enhance the health and well-being of children affected by this major social failure.

To begin with, pediatricians should screen for the social and economic risk factors that lead to homelessness in an effort to intercede before families are displaced. Children known to be in shelters or transient living conditions should be screened for mental health problems with standardized screening questionnaires such as the Screen for Child Anxiety Related Disorders (SCARED); the Ages & Stages Questionnaire: Social-Emotional (ASQ-SE); and the Patient Health Questionnaire (PHQ)-2 and PHQ-9.

Whether in an office setting or an emergency department, pediatricians should take advantage of acute care visits for homeless children to provide needed comprehensive care, for example, to update immunizations while dealing with the acute problem rather than scheduling a separate follow-up appointment.

As pediatricians, we care and advocate for our individual patients, but as citizens, recognizing the social underpinnings of homelessness, we can effect change in our communities through advocacy, political action, and work through various organizations, such as the American Academy of Pediatrics.

Any society is measured by how it cares for its most vulnerable members. To support our most vulnerable children we need programs that strengthen their families: through economic advancement by enhancing education and job skills; with agencies that support single-parent homes with subsidies for services such as after-school care; with early education available to every child. Social safety net programs (public assistance, WIC, SNAP, housing vouchers, and child care vouchers) enable young single parents to work while their children are in safe, positive environments. As always in pediatrics, prevention is preferable to treatment, and programs that address the social factors leading to homelessness can prevent the multitude of problems created for children who become homeless.

COMMENT: One hundred thousand or more children are homeless on any given night, and 2½ million children over the course of a year. This in "the land of the free," where, ironically, we call ourselves "the *home* of the brave"! Shame on us. And now, as I'm writing this in June 2018, we are fracturing families, separating children from their refugee parents at our borders—more than 2,000 children during the past 2 weeks, many of them not old enough to understand what is happening to them. What can we say? Shame on us.

Yes, advocacy is fundamental to the role of the pediatrician.

– Henry M. Adam, MD
Associate Editor, *In Brief*

CME Quiz Correction

An error appeared in the print version of the quiz accompanying the August 2018 review "Pediatric Esophageal Disorders: Diagnosis and Treatment of Reflux and Eosinophilic Esophagitis" (Adamiak T, Plati KF. *Pediatr Rev.* 2018; 39(8):392–402; DOI: 10.1542/pir.2017-0266). Question 5, answer option E should read "Two-food elimination diet consisting of animal milk and gluten-containing cereals followed by a step up to 4- or 6-food elimination diet in nonresponders." The online version of the quiz is correct, and a correction notice has been posted with the online version of the article. The journal regrets the error.

ANSWER KEY FOR OCTOBER 2018 PEDIATRICS IN REVIEW

Overall Approach to Trauma in the Emergency Department: 1. B; 2. C; 3. A; 4. E; 5. D.
Human and Animal Bites: 1. C; 2. C; 3. D; 4. D; 5. D.
Collagen Vascular Diseases: SLE, Dermatomyositis, Scleroderma, and MCTD: 1. A; 2. A; 3. C; 4. D; 5. A.

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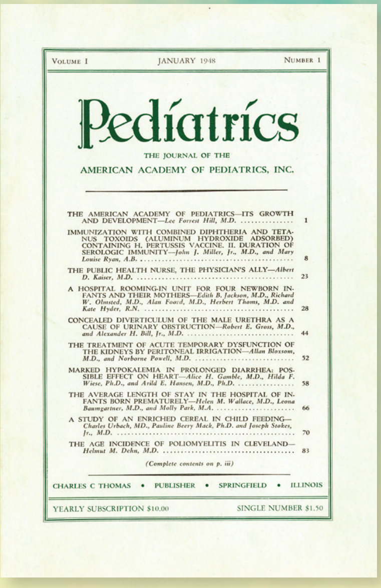

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Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC.

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Visual Diagnosis

An Uncommon Presentation of a Common Rash

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Sidney A. Palmer-Hill, MD*

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PRESENTATION

A 3-year-old boy is admitted to the hospital with rapid onset of a rash and swelling of the hands and feet. The rash began a day earlier, first noticed on the abdomen and legs, and spreading cephalad to the head, neck, and arms. His parents noted intermitted rhinorrhea for 1 week prior, without fever, cough, stridor, arthralgia, or myalgia. There was no evidence of dysphagia or odynophagia as he was eating and drinking normally. Immunizations were up to date, although he had not recently been immunized or taken any medications. The family lives on a farm where they spend significant time outdoors, noting daily contact with cows, pigs, and chickens and drinking unpasteurized milk. The parents did see a mosquito bite on his left temple the week before, which resolved without concern. The current rash was initially pruritic, responding to a dose of diphenhydramine. The medical history is notable for recurrent otitis media with placement of tympanostomy tubes and a single febrile seizure. His mother and maternal grandmother have seasonal allergies.

Physical examination reveals a mix of annular and polycyclic lesions (Fig 1), erythematous and blanching. Lesions appear in different stages, with earlier lesions having a dusky brown center (Fig 2). Nonpitting acral edema is noted, with no edema of the mouth or larynx. He has no stridor, cough, or wheezing. His mucous membranes are without ulcerations. Stroking of the skin on his back produces an erythematous wheal (Video).

DIAGNOSIS

Urticaria multiforme (UM) is a subtype of acute urticaria presenting with rapid onset of annular and polycyclic blanching wheals with dusky, discolored centers. The dusky centers may be visible after the erythema fades, but they resolve rapidly and do not leave permanent marks. Acral edema is common in younger children and may be accompanied by acrocyanosis. (1)(2)

Dermatographism, development of an erythematous wheal in response to stroking of the skin, is a common finding in UM. (1) Pruritus is a frequent complaint. (2)(3) Lesions vary in stage, and individual lesions resolve within 24 to 36 hours, (1) and resolution of the entire rash usually occurs within 2 weeks. (3)

DISCUSSION

Generally, UM results from a type 1 immunoglobulin E–mediated hypersensitivity, although in select cases it can occur from nonimmune triggering of mast

AUTHOR DISCLOSURE Drs Newman, Mowrer, Dunneback, and Palmer-Hill have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

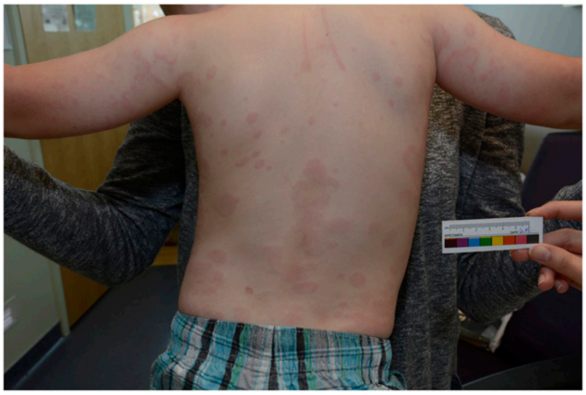


Figure 1. Erythematous polycyclic lesions. Note the dusky center in a central clearing of larger lesions. Linear lesions from stroking of skin are visible on the upper back.

cell degranulation by agents such as radiocontrast, aspirin, nonsteroidal anti-inflammatory drugs or opiates. Viral infections commonly precede the rash in younger children, whereas food and drug reactions are prominent in older children. Among medication reactions, penicillins are the most common trigger, followed by cephalosporins, sulfonamides, tetracycline, antiepileptic drugs, and monoclonal antibodies. (1)

In general, UM is a clinical diagnosis, and extensive laboratory investigation is not required for a diagnosis. Complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein level are generally normal. The immunoglobulin E level may be raised in some patients. Although biopsy is not generally recommended, histologic findings would be consistent with other forms of acute urticaria. (3)

Urticaria multiforme is frequently confused with erythema multiforme (EM) and serum sickness reactions. (1) Several features, on both physical examination and laboratory investigation, separate the 3 conditions. Common features of UM that are not seen in either EM or serum sickness reactions include a short lesion duration with prompt resolution of the rash, presence of acral edema, pruritus, and dermatographism. Laboratory findings, as noted earlier, are generally normal. Common causes of EM include infection, with herpes simplex virus-1 being the most common. Varicella and Epstein-Barr virus are also seen. In endemic areas, histoplasmosis may be a cause, as may be Kawasaki disease in a child with high fevers. Serum sickness is usually triggered by medication exposure. Both EM and serum sickness reactions feature fixed lesions generally taking weeks to resolve. Mucous membrane involvement is common in EM. High-grade fevers and arthralgias are more common in serum sickness. Both EM and serum sickness may present with an elevated white blood cell count and inflammatory markers. (3) Urticaria multiforme is a clinical diagnosis made on history and physical examination; routine laboratory tests are not indicated.

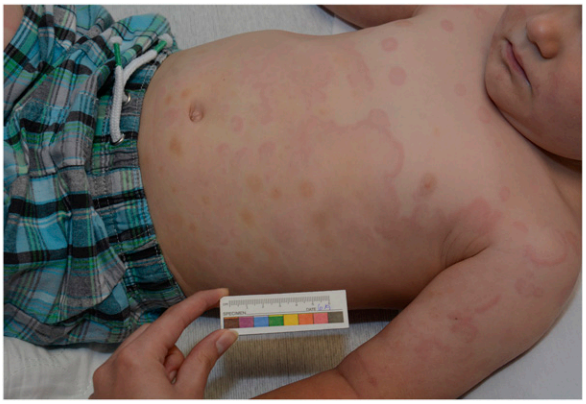
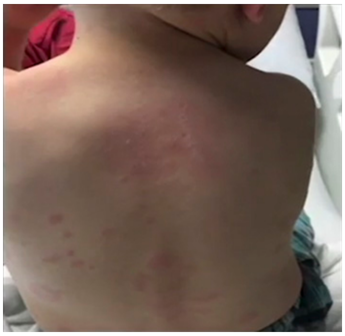


Figure 2. Dusky circular areas persist as initial lesions begin to fade over the abdomen.



Video. Stroking the back with a pen induces an erythematous flare, highlighting dermatographism.

Treatment of UM is aimed at discontinuing the offending agent, where known. Symptomatic treatment of pruritus is accomplished with antihistamines. In severe cases, systemic corticosteroids may be considered. (3) Cases lasting longer than 6 weeks are uncommon. Dermatology referral should be considered where appropriate.

PATIENT COURSE

Our patient's comprehensive metabolic panel, complete blood cell count, and C-reactive protein level were normal except for a white blood cell count of 17,290/μL (17.29$\times 10^9$/L) with neutrophilic predominance. Lyme antibodies were initially sent to the laboratory given the potential for tick exposure and were found to be negative. Results of a respiratory viral panel, including mycoplasma polymerase chain reaction, were negative. Although laboratory evaluation is not routinely indicated in UM, the emergency department physicians were concerned about undisclosed arthralgias. The patient was discharged from the hospital after 24-hour observation because he was clinically well and the rash began to resolve. On follow-up with his pediatrician after 4 days, complete resolution was noted. Ultimately, no etiology for his presentation was found.

SUMMARY

Urticaria multiforme is a form of acute urticaria presenting with annular and polycyclic lesions that are frequently confused with EM. Characteristic findings include rapid onset and resolution of lesions, acral edema, pruritis, and dermatographism on examination. Treatment is supportive only, consisting of antihistamines. Cases persisting longer than 6 weeks are uncommon, representing chronic urticaria, and referral to dermatology or an allergist should be considered. Diagnosis of UM is clinical and necessitates only a thorough physical examination.

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ONLINE

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Campylobacter Infections in Children

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Education Gap

Campylobacter is one of the 2 most common causes of foodborne illness in the United States. It most commonly occurs in children younger than 5 years of age. *Campylobacter* species can cause a wide range of syndromes, from asymptomatic infections to severe systemic infections.

Objectives

After completing this article, readers should be able to:

1. Recognize that *Campylobacter* is a common cause of foodborne illness in the United States and internationally.
2. Understand the indications for testing and the treatment of *Campylobacter* infection.

INTRODUCTION

Campylobacter species are an important cause of infection throughout the world, especially in young children. *Campylobacter jejuni* is the most common *Campylobacter* species in the United States, where it is 1 of the top 2 causes of foodborne illness. (1) Other important species include *Campylobacter upsaliensis*, *Campylobacter lari*, and *Campylobacter fetus*, which can cause serious systemic infections in all age groups, particularly in immunocompromised patients.

Campylobacter species infections cause gastroenteritis and typically present with diarrhea that may or may not be bloody, emesis, and abdominal pain. *Campylobacter* infection in children can mimic intussusception, appendicitis, or inflammatory bowel disease (IBD). Immune-mediated complications of *Campylobacter* infection include reactive arthritis and Guillain-Barré syndrome (GBS). *Campylobacter* infection is a nationally notifiable disease, and confirmed cases should be reported through the Centers for Disease Control and Prevention (CDC) Foodborne Diseases Active Surveillance Network.

Most *Campylobacter* infections are mild and self-limited and require only supportive care, although some may lead to severe dehydration. Serious infection or infections in immunocompromised hosts may benefit from treatment with macrolide antibiotics. Increasing rates of fluoroquinolone resistance have been observed in *Campylobacter* isolates. (2)

The largest source of *Campylobacter* infections is animals, especially wild and domestic birds. Strategies to prevent *Campylobacter* infection include thoroughly cooking poultry, preventing cross-contamination with other foods, properly

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ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CIDT	culture-independent diagnostic testing
GBS	Guillain-Barré syndrome
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
Ig	immunoglobulin

chlorinating water and pasteurizing milk, and practicing hand hygiene after interacting with animals.

MICROBIOLOGY

The *Campylobacter* genus is composed of gram-negative, motile, curved or spiral-shaped bacilli. The name *Campylobacter* is derived from Greek and Latin and means "curved rod." As of 2014, the genus included 26 species, approximately half of which cause disease in humans. (3) The organisms that are most commonly associated with infection in humans are *C jejuni* and *Campylobacter coli*. In 2015, 88% of all isolates that were speciated were *C jejuni*. (1) *C jejuni* contains 2 subspecies: *C jejuni* subspecies *jejuni* (typically referred to as *C jejuni*), which is the most commonly isolated cause of *Campylobacter* infection in the United States, and *C jejuni* subspecies *doylei*, which is much rarer. Other *Campylobacter* species that cause infection in humans are *C fetus, C upsaliensis, C lari*, and *Campylobacter hyointestinalis*. This review focuses on *C jejuni* and *C coli,* with a brief discussion of other, less common species at the end.

PATHOGENESIS

There are multiple organisms and host factors that enable *Campylobacter* infection in humans. Studies in healthy volunteers as well as observational data from outbreaks have demonstrated that the inoculum required to cause *Campylobacter* enteritis in humans can be as low as 500 organisms. (4)(5)(6) Disruption of the gastric acid barrier allows for pathogenic flora, such as *Campylobacter,* to survive and flourish. Therefore, patients with reduced gastric acidity, including those receiving proton pump inhibitors, may be at higher risk for infection with *Campylobacter.* (7)(8)(9)(10) The incubation period is relatively short, ranging from 1 to 7 days, with an average of 3 days. Higher inocula may result in shorter incubation periods. Infection is typically established in the distal ileum and colon and initially causes a noninflammatory diarrhea. This is followed by a locally invasive stage that leads to cell damage and inflammation that can present with dysentery, which is occasionally followed by translocation across the intestinal epithelium, causing lymphadenitis and extraintestinal infection. Histologically, infection is identical to salmonellosis or shigellosis and is marked by acute mucosal inflammation and edema, which can include infiltration of the lamina propria and crypt abscess formation. (11)(12)

The exact mechanisms of infection are not completely understood, but several virulence factors have been identified, including flagella, plasmids, adhesins, and chemotactic factors. (13) Initial infection is established when bacteria attach to intestinal epithelial cells via fimbriaelike filaments. Colonization of the gastrointestinal tract is then facilitated by flagella and chemotactic factors. *Campylobacter* flagellins do not seem to provoke proinflammatory cytokines, which may allow *Campylobacter* to evade innate immune response, differentiating it from other intestinal pathogens, including *Salmonella*. (14) There are a variety of other surface proteins and adhesins that facilitate colonization and invasion of intestinal epithelial cells. Some isolates of *Campylobacter* contain a high-molecular-weight plasmid, pVir, that has been associated with bloody stools and is thought to contribute to invasiveness. (15)

The immune response to *Campylobacter* infection seems to be primarily humoral. *Campylobacter*-specific serum immunoglobulin (Ig) A level rises rapidly during the first 2 weeks after infection and then declines slowly over the next month. The IgM and IgG antibody levels rise more slowly and peak 2 to 3 weeks after development of symptoms. (16) Prolonged and severe infection has been reported in patients with hypogammaglobulinemia. (17) The role of cellular immunity in *Campylobacter* infection is less well defined, but it does seem to be important because patients with human immunodeficiency virus (HIV) are also at risk for more severe and prolonged disease as well as higher rates of extraintestinal infection. (18) In immunocompetent patients, infection with *Campylobacter* provides some immunity against future infection, especially infection with the same strain.

EPIDEMIOLOGY

Campylobacter is a leading cause of acute diarrhea domestically and internationally. In the United States, *Campylobacter* and *Salmonella* are the 2 most common causes of foodborne illness. In 2016 the incidence of *Campylobacter* enteritis confirmed by culture or culture-independent diagnostic tests (CIDTs) was 17.4 infections per 100,000 persons, making it the most commonly identified cause of foodborne illness in the United States. *Campylobacter* has been tracked through the Foodborne Diseases Active Surveillance Network since 1996 and has been a notifiable disease since 2015. Most *Campylobacter* infections are mild and self-limited, but in 2016, 20% of reported infections resulted in hospitalization and 26 attributable deaths were identified (mortality, 0.3%). (19)

In the United States, the incidence of infection is highest in children younger than 5 years of age, but there is also a secondary peak in young adults. Infection rates are highest in the summer, and most infections are domestically acquired, although *Campylobacter* enteritis is also seen in returning international travelers. (1) In developing countries, the infection is hyperendemic, and symptomatic infection occurs almost exclusively in infants and young children, who can be infected repeatedly. Subsequent infections tend to be asymptomatic, making symptomatic disease rare in older children or adults. (20)(21)

Campylobacter enteritis is usually sporadic; only 0.4% of identified infections in 2015 were associated with an outbreak. (1) Transmission to humans occurs through ingestion of contaminated food or water or by direct contact with fecal material from infected people or animals. Animal reservoirs, including wild and domestic birds and other animals, are the most common source of *Campylobacter* infections. Multiple studies have shown that most broiler chicken flocks, 60% to 80%, may be contaminated with *Campylobacter* at slaughter. (22) The main vehicle of transmission to humans is improperly cooked poultry; 1 study suggested that 48% of *Campylobacter* infections are attributable to poultry exposure. (23) Direct acquisition of infection from animals is less common and is usually associated with occupational exposure to poultry. Infection has been reported in association with domestic pets, especially puppies and kittens, that have *Campylobacter* diarrhea. (23) In the fall of 2017 an outbreak of multidrug-resistant *Campylobacter* was linked to puppies sold through a national pet store chain. (24) Person-to-person transmission is rarer, but caretakers of children or other individuals in diapers are at increased risk. Sexual transmission has also been reported, especially in men who have sex with men. (25)

Outbreaks have been reported in association with the distribution of contaminated water or milk. *Campylobacter* can survive in water or milk for many weeks at low temperatures. Because *Campylobacter* is nearly ubiquitous in the environment, decontamination is the most important strategy to prevent transmission. Waterborne outbreaks have occurred in association with unchlorinated water or failed chlorination systems, and milk-associated outbreaks have been connected to raw milk or failures in the pasteurization process. (26)(27)(28)(29) Importantly, milk-borne outbreaks have been associated with raw milk that had passed routine testing because *C jejuni* can sometimes be difficult to culture. (29)

CLINICAL PRESENTATION

The most common illness caused by *C jejuni* and *C coli* is gastroenteritis. Children present with diarrhea and abdominal pain, often accompanied by vomiting and fever. Infection can result in significant dehydration. Bloody stools are also seen in at least half of infected children. (30)(31) Fevers can be prominent, and seizures, meningismus, and encephalopathy have all been reported in association with *Campylobacter* infection. (26)(32) Bacteremia is rare and is seen primarily in patients who are immunocompromised. (33)(18)

Perinatal *C jejuni* infection is rare but has been described. It can result in abortion, premature labor, and/or neonatal septicemia and meningitis. Symptomatic gastroenteritis in neonates is also possible, which may present with only grossly bloody stools or fever. Infection is generally acquired perinatally from mothers that shed *Campylobacter* either symptomatically or asymptomatically. Outbreaks in neonatal nurseries due to nosocomial spread have been reported. (34)

Campylobacter infection can also mimic other gastrointestinal illnesses. Infants with *Campylobacter* enteritis may present with only bloody stools and vomiting without fever, which can be mistaken for intussusception. In older children, acute *Campylobacter* ileocecitis can cause severe right lower quadrant pain without diarrhea mimicking appendicitis. (35)(36) *Campylobacter* enteritis most commonly progresses from the small bowel distally, but rarely patients with severe infection may present with only colitis and bloody diarrhea that can be confused with IBD. (37) Imaging can be helpful in excluding other intra-abdominal processes, such as intussusception. The acute inflammatory changes of *Campylobacter* infection observed on histologic analysis should help differentiate it from the chronic changes of IBD. It has also been suggested that *Campylobacter* infection may play a role in the development of IBD. (38)

Although the manifestations can be variable, *Campylobacter* gastroenteritis is usually relatively mild and self-limited, with symptoms lasting 24 to 48 hours in most patients. Excretion of the organism can last much longer than clinical symptoms. On average, shedding lasts 2 to 3 weeks, but it can range from 3 days to several months. (31) Shedding tends to be prolonged in younger children and patients with immunodeficiencies. Rarely, symptoms may persist for several weeks or relapse may occur after initial resolution. Chronic or recurrent infection is more common in immunocompromised patients, who can develop a prolonged relapsing syndrome that mimics IBD. This has been described in particular in patients with HIV, in whom long-term carriage and recurrent enteritis can be associated with bacteremia, fever, and debilitating illness. (18)(33)(39)(40)(41) The incidence of *Campylobacter* infection remains higher in patients with HIV than in the general population, but it has decreased significantly since the introduction of highly active antiretroviral therapy. (41)

COMPLICATIONS

Early Onset

Extraintestinal manifestations without enteritis are rare, but septic arthritis, bursitis, osteitis, and soft tissue infections have been reported. Acute extraintestinal complications of enteritis include cholecystitis, peritonitis in patients with peritoneal dialysis, septic pseudoaneurysm, pericarditis, and myocarditis. Erythema nodosum, glomerulonephritis, hemolytic anemia, IgA nephropathy, postinfectious irritable bowel syndrome, and intestinal perforation have all been described as well.

Late Onset

Late-onset immune-mediated complications of *Campylobacter* infection, including arthritis and GBS, have been well described.

Reactive arthritis after *Campylobacter* enteritis can occur 3 to 40 days (mean, 11 days) after the onset of diarrhea. It is usually oligoarticular and asymmetrical, and it predominantly affects the knees. It is more common and possibly more severe in patients with HLA-B27 phenotype. The development of arthritis does not seem to be related to the severity of the initial illness. Symptoms generally last for up to 21 days, and most patients have spontaneous recovery within 6 months without long-term sequelae. The arthritis is reactive, not infectious; synovial fluid is sterile. Arthritis occurs in up to 7% of patients, but as many as 20% of patients report arthralgia. (42)

Both serologic studies and culture surveys suggest that *Campylobacter* infection is the most commonly identified cause of GBS. Thirty percent to 40% of cases of GBS develop in patients who were infected with *Campylobacter* 10 to 14 days earlier. In the United States, 1 in 1,000 patients with *Campylobacter* enteritis goes on to develop GBS. Some studies have suggested that GBS associated with *Campylobacter* infection may have a poorer prognosis than GBS associated with other etiologies. (43)

The primary mechanism for *Campylobacter*-associated GBS is molecular mimicry. The *C jejuni* lipopolysaccharide resembles GM1 ganglioside on peripheral nerve myelin. Infection can lead to the development of cross-reacting antibodies that cause nerve damage. The Miller Fisher variant of GBS, with more prominent cranial nerve involvement resulting in ophthalmoplegia, areflexia, and ataxia, is also more common in patients with *Campylobacter* infection. It is thought to be caused by antibodies that cross-react with *Campylobacter* lipopolysaccharide and ganglioside GQ1b in cranial nerve myelin. (44) Certain *Campylobacter* serotypes, especially Penner O19 and O41, seem to be more commonly associated with GBS. (43) There may be factors other than molecular mimicry that also play a role in the development of *Campylobacter*-associated GBS. Additional host factors seem to be important; some patients develop antibodies to GM1 ganglioside but do not develop neurologic symptoms. There may be an association between HLA types and the development of *Campylobacter*-associated GBS. (45)

DIAGNOSIS

Campylobacter enteritis is often clinically indistinguishable from other viral or bacterial gastroenteridites. Diagnostic testing is not always indicated for children who present with acute diarrheal illnesses, with or without fever or vomiting, because determining the cause often does not change clinical management. However, Infectious Diseases Society of America guidelines suggest testing patients with fever or bloody diarrhea or others in whom treatment may be indicated, including anyone with immunodeficiencies. In addition, organism-specific diagnosis can be valuable for the management of outbreaks. Blood cultures are recommended in infants younger than 3 months of age, those with signs of sepsis or systemic manifestations, and immunocompromised patients. (46)

Stool culture is the gold standard for the identification of *Campylobacter* species. Most laboratories specifically look for *Campylobacter* in standard stool cultures, but it can be difficult to isolate. *Campylobacter* grows best on media containing selective antibiotics and in microaerobic conditions with 5% to 10% oxygen, 1% to 10% carbon dioxide, and some hydrogen. *C jejuni* and *C coli* grow best at 107.6°F (42°C). *Campylobacter* is identified by its characteristic appearance as a comma- or spiral-shaped Gram-negative bacillus as well as oxidase and catalase production. Species-level identification is not typically performed, and differentiation of *C jejuni* from *C coli* is not usually necessary for management. Speciation and strain typing can be helpful for epidemiologic purposes or when species other than *C jejuni* or *C coli* are suspected. This typing is typically performed at reference laboratories.

Use of CIDTs, including nucleic acid amplification tests, is increasing. (19) These tests are generally more sensitive and have faster turnaround times than traditional culture-based diagnostics. Reverse transcriptase polymerase chain reaction identifies *Campylobacter* from stool 20% to 40% more frequently than culture-based methods. (47) However, because these tests identify the presence of nucleic acid rather than viable organisms, the clinical significance is not always clear. The identification of multiple pathogens is not uncommon and can be difficult to interpret. In addition, CIDTs cannot be used to identify antibiotic susceptibility patterns. Unlike organisms such as *Shigella* and *Salmonella*, cultures of *Campylobacter* often are not performed automatically when the organism is detected by CIDT. Antibiotic resistance to quinolones and tetracyclines is common in *Campylobacter* isolates, so if treatment is warranted and there is concern for resistance, cultures can still be beneficial after identification by CIDT. (2)

Serologic testing can be used to detect recent *Campylobacter* infection in patients with reactive arthritis or GBS who have negative stool studies. Serologic studies are not helpful in the diagnosis of acute *Campylobacter* infection.

If *Campylobacter* infection is suspected or confirmed, it is important to attempt to identify the source of infection, mostly to prevent others from becoming infected. Families should be asked about exposures, including consumption of raw milk or contaminated drinking water, undercooked meats or poultry, contaminated fruits or vegetables, and contact with animals (wild and domesticated fowl, puppies, kittens) or their feces. Travel exposure may also be relevant, although most infections are acquired domestically.

MANAGEMENT

Campylobacter infection typically results in a mild, self-limited enteritis that requires only supportive care. Adequate rehydration, either orally or intravenously, is the mainstay of acute management. Antimotility agents should be avoided due to prolongation of symptoms. (48) Several trials have suggested that probiotics may decrease diarrhea duration and stool frequency in immunocompetent children with gastroenteritis of any cause, although the effect seems to be greater in viral than bacterial gastroenteritis, and the optimal formulation remains unknown. This benefit also has to be weighed against case reports of bacteremia or fungemia with molecularly matched isolates in critically ill or immunocompromised patients who received probiotics. (49) In countries with a high prevalence of zinc deficiency or malnutrition, zinc supplementation reduces the duration of diarrhea in children 6 months to 5 years of age with acute diarrhea. (50)

A meta-analysis of 11 randomized controlled trials of antibiotic treatment versus placebo for the treatment of *Campylobacter* infections in children and adults showed that antibiotic treatment reduced the duration of symptoms by 1.3 days and the duration of *Campylobacter* excretion in stool. However, given the self-limited nature of most *Campylobacter* infections, the relatively modest benefit to treatment with antibiotics, and the risk of development of antibiotic resistance, treatment of uncomplicated infection is usually not recommended. (51) Treatment is recommended in patients with severe disease, which includes those with bloody stools, high fever, extraintestinal infection, worsening or relapsing symptoms, or prolonged symptoms that exceed 1 week. It is also recommended for patients with uncomplicated infection who are elderly, pregnant, or immunocompromised due to their risk of severe disease. Both GBS and other late-onset complications of *Campylobacter* infections are immune-mediated and usually develop once symptoms of acute infection have resolved. Therefore, antibiotics are not routinely included in the management of these *Campylobacter*-associated syndromes unless patients otherwise meet the criteria for treatment with antibiotics, including prolonged or severe symptomatic infection or immunocompromise.

In patients with uncomplicated infection who merit antibiotic therapy, the recommended treatment is azithromycin 10 mg/kg per day for 3 days or erythromycin 40 mg/kg per day in 4 divided doses for 5 days. Treatment usually eradicates *Campylobacter* from the stool within 2 to 3 days. (52) A longer course (7–14 days) may be necessary in complicated infections or in patients who are immunocompromised. Carbapenems are appropriate empirical treatment in patients who are severely ill and unable to tolerate oral treatment, although it is important to complete susceptibility testing to verify carbapenem activity. Treatment for bacteremia should be tailored to available susceptibility testing. Although *C jejuni* and *C coli* are usually sensitive in vitro to clindamycin, tetracyclines, and chloramphenicol, data are lacking to support their use clinically. *Campylobacter* species are inherently resistant to trimethoprim and β-lactam antibiotics, including penicillin and cephalosporins, so these should be avoided.

Resistance

Fluoroquinolones may also be effective treatment for *Campylobacter* infection, but resistance is increasingly common, limiting the effectiveness of these agents for this indication. In the past, this resistance was thought to be, in part, attributable to quinolone use in poultry feeds, but this practice has been banned in the United States since 2005. United States data from 2014 indicated that ciprofloxacin resistance was present in 27% of *C jejuni* isolates and 36% of *C coli*. (2) Resistance is significantly higher outside the United States and is important to consider in travelers. (53) Fortunately, macrolide resistance remains rare in the United States.

PREVENTION

Prevention of *Campylobacter* infection should focus on transmission from animals, milk or waterborne disease, and person-to-person transmission. Contaminated poultry is the most common source of *Campylobacter* infection, so thoroughly cooking poultry and avoiding cross-contamination with other foods should be emphasized. *Campylobacter* is killed by heat, so all meat, but especially chicken, should be cooked to proper temperature. Hand hygiene and thorough cleansing of cutting boards and utensils after contact with raw poultry as well as avoiding contact between raw poultry and other foods are also important. Hand hygiene is also important after contact with the feces of dogs and cats, especially puppies and kittens, where high rates of *Campylobacter* carriage are present. Unpasteurized milk should be avoided, and water should be chlorinated.

People with diarrhea should be excluded from food handling and the care of patients in hospitals and child care centers. They can resume work if infected but asymptomatic, as long as proper hand hygiene is practiced.

Infants and children in diapers who are found to have *Campylobacter* enteritis should be excluded from child care centers until symptoms have resolved. Treatment of these children with azithromycin or erythromycin can be considered to limit spread. Contact precautions should be used for children who are hospitalized with symptomatic *Campylobacter* enteritis. (52) Many institutions use syndromic contact isolation for any patient with diarrhea, regardless of the cause.

Previous infection with *Campylobacter* decreases the risk of future symptomatic infection but is not completely protective, so patients with previous infections should still use the prevention measures detailed previously herein.

OTHER *CAMPYLOBACTER* SPECIES

Campylobacter upsaliensis

Similar to *C jejuni* and *C coli*, *C upsaliensis* usually causes gastroenteritis, which may present as bloody diarrhea in 25% of patients, and occasionally bacteremia. It can also occasionally cause vomiting but is usually milder than *C jejuni* infection. (54) Bacteremia is primarily seen in malnourished or immunocompromised patients. (55) It is more common in children than adults. *C upsaliensis* was initially isolated from dogs, and they are considered to be its primary reservoir. Infection may be associated with close contact with dogs.

C upsaliensis is catalase negative or catalase weak and has a different antibiotic susceptibility pattern than *C jejuni*. It is susceptible to antibiotic agents usually used in *Campylobacter*-selective media and is, therefore, not detected in cultures using these media. (56) Consequently, the true prevalence of *C upsaliensis* is not clear, but it is the third most common *Campylobacter* species (after *C jejuni* and *C coli*) recovered in foodborne infections in the United States. (1)

Data are limited regarding treatment of *C upsaliensis*. Similar to *C jejuni* and *C coli*, it is usually treated with macrolides, although resistance has been reported in some studies. Some isolates are susceptible to gentamicin, azithromycin, erythromycin, meropenem, cephalosporins, fluoroquinolones, tetracyclines, and aminoglycosides. (57)

Campylobacter lari

C lari is the fourth most commonly isolated *Campylobacter* species in foodborne illnesses. It is common in chickens but relatively rare in humans. It accounts for less than 1% of *Campylobacter* isolates from humans and is predominantly seen in immunocompromised patients and neonates. (58) It can be grown on conventional *Campylobacter*-selective agars under similar conditions as *C jejuni*. Macrolides are generally effective for treating *C lari* infections.

Campylobacter fetus

C fetus is rare but tends to cause more serious illness than *C jejuni or C coli*. It causes bloodstream infections more commonly than gastroenteritis and is more common in patients at the extremes of age. In 2015 only 0.1% of laboratory-confirmed cases of *Campylobacter* in the United States were due to *C fetus*, but studies have shown that it is responsible for 19% to 53% of *Campylobacter* bacteremia. (1)(33)(59) It may not be identified in stool cultures because it grows best at 77.0°F (25°C) and 98.6°F (37°C) rather than at 107.6°F (42°C) like *C jejuni*. (60)

Three syndromes associated with *C fetus* bloodstream infection have been described: first, isolated bloodstream infection that is self-limited or rapidly responds to antibiotic therapy; second and most commonly, bloodstream infection associated with a focal infection such as meningitis, pneumonia, endocarditis, or thrombophlebitis; third, chronic relapsing/remitting bacteremia, seen most commonly in immunocompromised patients. Perinatal infection has also been described and can be associated with spontaneous abortion, preterm labor, and neonatal septicemia or meningitis. Perinatal infection with *C fetus* is rare but tends to be more severe than with *C jejuni*.

Although *C fetus* is often susceptible to ampicillin and gentamicin, carbapenems are preferred first-line agents pending susceptibility testing. *C fetus* is typically susceptible to ampicillin, extended-spectrum cephalosporins, meropenem, imipenem, aminoglycosides, and erythromycin. (61)

Summary

- On the basis of strong evidence, *Campylobacter* is a common cause of acute diarrhea throughout the world, and *Campylobacter jejuni* is the most commonly isolated *Campylobacter* species. (1)
- On the basis of strong evidence, most *Campylobacter* infections result in a mild, self-limited enteritis, but *Campylobacter* can also cause invasive disease, including bacteremia. *Campylobacter* is also the most commonly identified cause of Guillain-Barré syndrome and can cause reactive arthritis.
- Based on strong clinical evidence, stool culture remains the gold standard for the diagnosis of *Campylobacter* infection, but culture-independent diagnostic testing is also sensitive. On the basis of consensus, species-level identification of *Campylobacter* isolates is usually not necessary for clinical management.
- *Campylobacter* is a nationally notifiable disease. Any confirmed cases should be reported through the Centers for Disease Control and Prevention Foodborne Diseases Active Surveillance Network.
- Based on strong evidence, antibiotic treatment of *Campylobacter* infections results in a modest reduction of duration of infection (1 day) and a reduced duration of shedding. However, based on consensus, treatment is not recommended for uncomplicated infection in immunocompetent hosts due to the mild nature of infection, modest benefit, and risk of development of antibiotic resistance. Treatment with azithromycin or erythromycin is recommended for severe infections or infections in immunocompromised hosts.
- Based on an abundance of evidence, important practices for the prevention of *Campylobacter* infection are thoroughly cooking poultry, avoiding cross-contamination between poultry and other foods, chlorination of water, pasteurization of milk, and observation of hand hygiene after contact with animals and their feces.

References for this article are at http://pedsinreview.aappublications.org/content/39/11/533.

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1. A 7-year-old previously healthy girl presents to your office with a 3-day history of watery diarrhea. The mother reports that the child has also had several episodes per day of nonbloody, nonbilious emesis and some abdominal pain. Two other immediate family members have had similar symptoms for the past few days, including the father and the child's older brother. On further history, the mother tells you that they visited relatives in Maine approximately 2 weeks ago, swam in a lake, and went to a petting zoo. They have 2 healthy dogs in the home. The family members consume only pasteurized milk and cheeses but the child does drink a lot of milk both at home and at school. The family went to a new restaurant approximately 3 days before the onset of symptoms where they shared several dishes, including chicken and steak. Given the patient's recent exposures, you decide to test her stool for enteric pathogens, and testing returns positive for *Campylobacter.* Which of the following is the most likely mode of transmission of *Campylobacter* in this child?
    - A. Adult pets such as dogs and cats.
    - B. Exposure to lake water.
    - C. Improperly cooked poultry.
    - D. Pasteurized milk and cheeses.
    - E. Petting zoos.
2. A 5-year-old girl is admitted to the hospital with dehydration after 2 days of nonbilious, nonbloody emesis, several episodes of bloody diarrhea, and fever today to 101.5°F (38.6°C) after drinking raw milk. During the hospital stay she is found to be positive for *Campylobacter jejuni.* Her parents are very concerned about her condition and ask you what some of the complications of this infection are. Which of the following would be considered a late-onset complication of *Campylobacter* infection?
    - A. Encephalitis.
    - B. Guillain-Barre syndrome (GBS).
    - C. Hemolytic anemia.
    - D. Immunoglobulin A nephropathy.
    - E. Myocarditis.
3. A previously healthy 12-year-old girl is brought to the clinic with new-onset ataxia. She reports a gradual onset of the ataxia and lower extremity weakness over the course of the past 2 days. She is afebrile and her vital signs are stable. She is found to be areflexic in her lower extremities. A head computed tomographic scan is performed and the results are normal. She reports a history of nonbloody diarrhea, emesis, and abdominal pain that lasted 4 days approximately 2 weeks earlier after her family visited a farm. You are concerned that she might have *Campylobacter*-associated GBS. You discuss this entity with the family. Which of the following best describes *Campylobacter*-associated GBS?
    - A. *Campylobacter fetus* is the most common type of *Campylobacter*-associated GBS.
    - B. *Campylobacter* infection is the most commonly identified cause of GBS.
    - C. Carries a better prognosis than GBS associated with other etiologies.
    - D. Considered to be an early-onset complication of *Campylobacter.*
    - E. Its primary mechanism is direct invasion of the nerve roots.
4. A 13-year-old boy is brought to the clinic with a 3-day history of watery, nonbloody diarrhea. The patient and his father recently returned from a camping trip in North Carolina 1 week earlier where they believe they may have had some undercooked poultry. The child has had 2 or 3 episodes of watery stools per day and 1 episode of nonbilious, nonbloody emesis this morning. He reports mild abdominal pain that is relieved after having a bowel movement. He has a poor appetite, decreased oral intake, and slightly decreased urine output. On physical examination the patient is in no apparent distress. His temperature is

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99.5°F (37.5°C); heart rate, 103 beats/min; respiratory rate, 20 breaths/min; and blood pressure, 90/60 mm Hg. His abdomen is mildly tender in the periumbilical area, but there are normal bowel sounds and no masses or hepatosplenomegaly. The remainder of his examination findings are within normal limits. Which of the following is the next best step in the management of this patient?

A. Antimotility agent.
B. Empirical treatment with azithromycin.
C. Stool sample for culture.
D. Trial of an oral rehydration solution.
E. Zinc supplementation until diarrhea resolves.

5. A 3-year-old child is brought to the emergency department (ED) with a 5-day history of watery stools that have now turned grossly bloody, with up to 12 stools reported on the day of admission. The parents report that the child had 4 or 5 episodes of emesis and complained of abdominal pain that worsened today along with a fever (to 103.6°F [39.8°C]), prompting them to come to the ED. On further history, the parents report that they went to a local farm recently and drank raw milk. You have seen several other patients in the past few days who visited this same farm with symptoms of gastroenteritis. Two of the patients had positive stool cultures for *Campylobacter*. On examination the child is ill appearing, pale, and lethargic. His temperature is 104.2°F (40.1°C), heart rate is 150 beats/min, respiratory rate is 40 beats/min, and blood pressure is 75/35 mm Hg. The child's lips are dry. His lungs are clear to auscultation and his heart sounds are normal, but he is tachycardic. On abdominal examination, he moans on palpation of his abdomen. Bowel sounds are sluggish throughout. His extremities are cool and his capillary refill is 4 to 5 seconds. Immediately, intravenous access was obtained and the child was given a normal saline bolus and was admitted to the PICU, where empirical antibiotics were started. Which of the following is the most appropriate choice of empirical antibiotic therapy?

A. Ampicillin.
B. Ceftriaxone.
C. Ciprofloxacin.
D. Meropenem.
E. Trimethoprim-sulfamethoxazole.

Pediatric Gastritis, Gastropathy, and Peptic Ulcer Disease

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Education Gap

Providers should be able to identify the signs and symptoms of peptic ulcer disease in children, select the proper diagnostic tests needed to confirm the diagnosis, and describe adequate treatment regimens to start once the diagnosis is confirmed.

Objectives

After completing this article, readers should be able to:

1. Understand the mechanism and pathogenesis of gastritis, gastropathy, and peptic ulcer formation.
2. Recognize the symptoms of and risk factors for gastritis, gastropathy, and peptic ulcer disease.
3. Understand which patients warrant referral to a gastroenterologist for possible endoscopy.
4. Review the role of *Helicobacter pylori* in peptic ulcer disease.
5. Review the treatment of peptic ulcer disease with and without the presence of *H pylori*.

INTRODUCTION

Gastritis, gastropathy, and peptic ulcer disease (PUD), collectively known as acid peptic disease, are often described as a spectrum of the same disease. Although these conditions are more common in adults, their incidence in the pediatric population is clinically significant. Left untreated, gastritis can progress to PUD, which can result in serious complications such as perforation, bleeding, bowel strictures, and obstruction. Studies describing the role of *Helicobacter pylori*, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and other causes have helped to further expand our understanding of gastritis and PUD in children. Direct visualization and the ability to biopsy with endoscopy have revolutionized the diagnosis and treatment of these diseases.

EPIDEMIOLOGY

The incidence of PUD in children is lower than that in adults. Based on several international studies, the incidence in children varies from 2% to 8%. (1)(2) The

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ABBREVIATIONS

H2RA	histamine 2 receptor antagonist
IBD	inflammatory bowel disease
NSAID	nonsteroidal anti-inflammatory drug
PPI	proton pump inhibitor
PUD	peptic ulcer disease

incidence of bleeding ulcers is lower and is estimated to be between 0.5 and 4.4 of 100,000 individuals. (3) These rates are increased with the use of NSAIDs, corticosteroids, and immunosuppressive medications. The prevalence is similar between both sexes, with the incidence of PUD increasing after age 10 years. (4) Racial and ethnic differences have been noted in the pediatric population, with non-Hispanic black and Mexican American populations being more affected than white populations. (5)

PATHOGENESIS

The intestinal mucosa is composed of 3 layers: epithelium, lamina propria, and muscularis mucosa. Gastritis is described as the presence of inflammatory cells. Gastropathy occurs when there is gastric mucosal damage with no inflammatory cells. (2) Peptic ulcers occur when gastric or duodenal inflammation leads to defects of the muscularis mucosa. The acidic gastric contents, which normally aid in digestion, become corrosive when there is an increase in acid production or a disruption of protective factors. Parietal cells of the stomach produce gastric acid via proton pumps (H^+/K^+ ATPase) in response to acetylcholine from vagal efferents, histamine from enterochromaffin cells, and gastrin from G cells.

There are several mechanisms to protect the gastric mucosa, including a mucus layer, a pH-neutral buffer zone, an epithelial layer, and a rich gastric blood supply. The mucus layer is composed of mucin secreted by surface foveolar cells. This mucus layer acts as a diffusion barrier and overlies a pH-neutral buffer zone composed of bicarbonate secreted by epithelial cells. Prostaglandin release mediates mucin secretion from surface foveolar cells and bicarbonate release from epithelial cells. Epithelial cells have tight junctions that act as an additional barrier of protection. A rich gastric blood supply redistributes excess protons that reach the lamina propria. Ultimately, peptic ulcers are formed when the damaging factors overcome the protective mechanisms. (6)

PRESENTATION AND INITIAL EVALUATION

Symptoms of acid peptic disease vary by the age of the patient. Younger patients can present with irritability, poor feeding, regurgitation, vomiting, gastrointestinal bleeding, or poor weight gain. Older patients can present with dull or diffuse abdominal pain, gas, bloating, nausea, or nocturnal awakenings from abdominal discomfort. It is nearly impossible to differentiate between gastric and duodenal ulcers based on history alone. However, gastric ulcers classically present with epigastric gnawing or burning immediately after meals and duodenal ulcers present with pain 2 to 3 hours after meals. Severe presentations of PUD can include intestinal perforation, severe gastrointestinal bleeding with erosion of vasculature, or pancreatitis with posterior intestinal erosion. The differential diagnosis for epigastric and periumbilical abdominal pain extends beyond acid peptic disease. Clinicians must also consider and rule out pancreatitis, appendicitis, celiac disease, lactose intolerance, inflammatory bowel disease (IBD), and parasitic infections. (6)

The initial evaluation of a patient with suspected acid peptic disease should begin with a thorough history. Special attention must be given to the onset and duration of symptoms and alleviating and exacerbating factors. Evaluation of medical history for conditions that predispose to PUD should be noted, including an assessment of medication use. Social and dietary history will also provide clues to predisposing factors. Family history, especially that of *H pylori* or gastritis, is crucial to ascertain.

ETIOLOGIES

The common causes of peptic ulcers include *H pylori*, medication use, and stress-related gastric injury. Less common causes include ingestion of corrosive substances, hypersecretory states (Zollinger-Ellison syndrome), IBD, systemic mastocytosis, chronic renal failure, and hyperparathyroidism. (6)

Infectious

There are many infectious causes for acid peptic disease. The most common bacterial cause is *H pylori*. Less common infectious etiologies include viruses (cytomegalovirus, Epstein-Barr virus), fungi (*Candida albicans*, histoplasmosis, and *Cryptosporidium*), and parasites (*Giardia lamblia*, ascariasis).

Medications

High-dose corticosteroids and NSAIDs disrupt prostaglandin production, leading to decreased bicarbonate and mucin production, compromising mucosal protection. Less commonly, gastritis has been identified with the use of valproic acid, chemotherapeutic agents, and iron supplementation.

Stress and Trauma

Stress-related gastric injury occurs in patients with severe physiologic stress due to trauma, burns, intracranial disease, major surgery, or serious medical disease. The pathogenesis of stress-related gastric injury is most likely related to local ischemia from splanchnic vasoconstriction or systemic hypotension. Local ischemia disrupts the redistribution of protons, leading to a more acidic milieu that is more prone to ulcer formation. Intracranial disease can cause direct stimulation of vagal nuclei, resulting in acid hypersecretion. Physical trauma from compression of gastric mucosa at the level of a hiatal hernia is the cause of a specific type of ulcer known as Cameron ulceration. Other forms of physical trauma include ingestion of corrosive substances, such as strong acids and bases, that directly damage mucosal cells.

Endocrine

Excess gastrin and histamine lead to acid hypersecretion and consequent ulcer formation. (6) Zollinger-Ellison syndrome results from the uncontrolled release of gastrin by a tumor. Inflammatory bowel disease results in increased levels of gastrin and histamine. (7)(8) In systemic mastocytosis, there is an excessive production of histamine. In chronic renal disease and hyperparathyroidism, hypercalcemia stimulates gastrin production.

PHYSICAL EXAMINATION

The initial step of examination includes evaluation of vital signs, including weight and height. It is important to determine appropriate growth trajectory. The *Z*-scores, standard deviations from the mean, for weight-for-height and/or BMI should be calculated. If the patient has a poor growth trajectory or *Z*-scores less than −1, this might indicate the presence of chronic disease or poor nutrition. There are no focal findings specific for acid peptic disease. Examination of the oropharynx should include evaluation of dentition for caries and eroded enamel that may indicate frequent vomiting or reflux. Pale conjunctiva, tachycardia, or flow murmur may indicate anemia associated with chronic disease or blood loss. Halitosis with regurgitation or dysphagia may indicate achalasia. Examination of the lungs may reveal wheezing, which can be seen from bronchospasm-associated chronic reflux.

Abdominal examination should focus on determining areas of tenderness. Hepatomegaly and splenomegaly should also be ruled out. Rectal examination should determine the presence of fissures or rectal skin tags, which may be seen in Crohn disease. Fecal occult blood may also be useful for determining the presence of a gastrointestinal bleed. Potential extraintestinal manifestations of IBD should be noted on physical examination, including joint swelling, skin rashes, oral lesions, and eye abnormalities.

LABORATORY STUDIES

Initial laboratory examination should be tailored to the patient's presenting symptoms. A complete blood cell count may show leukocytosis or thrombocytosis, which can provide information about systemic inflammation. The presence of anemia can indicate blood loss or chronic disease. An electrolyte panel may show hypercalcemia, hypophosphatemia, and hyperchloremic acidosis, which are characteristic of hyperparathyroidism. A low albumin level may indicate poor nutritional status or decreased production related to chronic inflammatory states. An elevation in transaminases may point to viral etiologies. Inflammatory markers (ie. erythrocyte sedimentation rate and C-reactive protein) are also helpful, but these may not be specific. Infectious sources of symptoms should be ruled out, especially in immunocompromised patients. For example, cytomegalovirus may be identified by use of serum or urinary polymerase chain reaction. Stool studies, including ova and parasites, cultures, and polymerase chain reaction, may identify other etiologies.

ROLE OF UPPER ENDOSCOPY

Certain signs and symptoms associated with acid peptic disease are an indication for gastroenterology referral for possible endoscopic evaluation (Table 1). Upper endoscopy has been well described as a superior diagnostic study for PUD compared with radiography. (9) It is important to note that not all patients with abdominal pain require upper endoscopy. The decision to proceed with endoscopy should be made only if the outcome of the test will change current patient management. An assessment of risks and benefits of endoscopy should be discussed with the patient and family.

Endoscopy is the diagnostic test of choice when IBD is suspected. The gastroenterologist may be able to grossly identify aphthous ulcers and other luminal manifestations of Crohn disease, ulcerative colitis, and indeterminate colitis.

TREATMENT

Initial treatment of acid peptic disease includes discontinuation of offending agents and treatment of underlying

TABLE 1. **Indications for Upper Endoscopy**

Refractory anemia	Upper gastrointestinal bleeding
Refusal to eat	Odynophagia
Dysphagia	Constitutional symptoms
Pain despite acid suppressant therapy	Intractable vomiting

etiologies. Acid suppression is an effective strategy to alleviate symptoms and promote ulcer healing. Available agents on the market include histamine 2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). Commonly used drugs and their doses are listed in Table 2. The H2RAs are associated with tachyphylaxis and rebound symptoms. (10) For this reason, some clinicians use PPIs if prolonged therapy is needed. There is mixed evidence regarding ideal dosing of PPIs in children and adolescents.

The mechanism of action of H2RAs is reversible and competitive inhibition of H2 receptors on gastric parietal cells. Two commonly used agents are famotidine and ranitidine. A third agent, cimetidine, is less recommended because it can inhibit cytochrome P450 enzymes, leading to decreased metabolism of other drugs. Minor adverse effects include diarrhea, headache, and fatigue. (11)

The PPIs are prodrugs that are activated in an acidic environment and subsequently bind irreversibly to the H^+/K^+ ATPase. Available agents include omeprazole, esomeprazole, pantoprazole, and lansoprazole. The PPIs are preferred over the H2RAs for the treatment of PUD and NSAID-induced ulcers. Generally these drugs are well tolerated. Adverse effects include headache, nausea, abdominal pain, and altered bowel habits. (11) There are studies

TABLE 2. **Acid Suppressant Drugs and Their Doses**

DRUG	TYPE	GENERAL DOSING	DOSE FOR ULCERS	DOSAGE FORMS (ORAL)
Ranitidine	H2RA	5–10 mg/kg per day divided twice daily; if age >16 y can use 150 mg BID; maximum dose is 300 mg/d for GERD and 600 mg/d for erosive esophagitis	4–8 mg/kg per day divided twice daily; if age >16 y can use 150 mg BID; maximum 300 mg/d	15 mg/mL of syrup 75-mg tablet 150-mg tablet or capsule 300-mg tablet or capsule
Famotidine	H2RA	0.5–1 mg/kg per day divided twice daily (infants aged 1–3 mo use only daily); if age >17 y may use 20–40 mg BID (higher dose for worse symptoms)	0.5–1 mg/kg per day divided twice daily; if age >17 y can use 20 mg BID	40-mg/5-mL suspension 10-mg tablet 20-mg tablet 40-mg tablet
Omeprazole	PPI	5 to <10 kg: 5 mg once daily 10 to <20 kg: 10 mg once daily ≥20 kg: 20 mg once daily	No specific dosing guidelines for PUD in pediatric patients	2-mg/mL suspension 10-mg capsule 20-mg tablet or capsule 40-mg capsule 2.5-mg packet 10-mg packet
Lansoprazole	PPI	Infants: 1–2 mg/kg per day Children: 0.7–3.0 mg/kg per day Fixed dosing: Age ≥3 mo: 7.5 mg BID Age 1–11 y: 15 mg/d if ≤30 kg; 30 mg/d if >30 kg Age ≥12 y: 15 mg/d	No specific dosing guidelines for PUD in pediatric patients	3-mg/mL suspension 15-mg capsule or disintegrating tablet 30-mg capsule or disintegrating tablet
Pantoprazole	PPI	Children aged 1–5 y: 0.3, 0.6, 1.2 mg/kg per day Children aged ≥5 y: ≥15 to <40 kg: 20 mg once daily for up to 8 wk ≥40 kg: 40 mg once daily for up to 8 wk	No specific dosing guidelines for PUD in pediatric patients	20-mg tablet 40-mg tablet or packet
Esomeprazole	PPI	Infants to children aged <12 y: 3–5 kg: 2.5 mg once daily >5–7.5 kg: 5 mg once daily >7.5–20 kg: 10 mg once daily >20 kg: 10 or 20 mg once daily Patients aged ≥12 y: 20–40 mg once daily	No specific dosing guidelines for PUD in pediatric patients	2.5-, 5-, 10-, 20-, or 40-mg oral packet 20- or 40-mg delayed-release capsule 20-mg delayed-release tablet

BID=twice daily, GERD=gastroesophageal reflux disease, H2RA=histamine 2 receptor antagonist, PPI=proton pump inhibitor, PUD=peptic ulcer disease.

that associate the use of PPIs with increased incidence of fractures, (12) *Clostridium difficile*, (13)(14) and hospital-acquired pneumonia in the adult population. The association with pneumonia, however, is thought to be in part due to confounding factors. (15)

Sucralfate is a sucrose sulfate and aluminum hydroxide salt that creates a gel over the mucosal surface that protects from acid injury. It has little systemic absorption and, therefore, few adverse effects. Sucralfate should be used with caution in patients with renal failure due to risk of aluminum toxicity. Another coating agent is bismuth. It is used frequently as part of *H pylori* infection eradication therapy.

A less used drug in the pediatric population is misoprostol, a prostaglandin E analogue that can be used to prevent and treat NSAID-induced ulcers. One common reported adverse effect is diarrhea. (11)

In the critically ill population, stress ulcer prophylaxis is widely used. Although the available evidence is rated low quality, the 2016 Surviving Sepsis campaign recommends use of either PPIs or H2RAs in patients with a high risk of bleeding, such as patients who require mechanical ventilation for more than 48 hours and those with coagulopathy. (16)

Due to advances in the understanding of the pathophysiology of PUD, medical therapy is now the mainstay of management. Today, surgical procedures to treat PUD (eg, selective vagotomy) are rarely performed. The role of surgical treatment is primarily in the management of complications from PUD, such as gastrointestinal bleeding and perforation.

Some clinicians may recommend dietary restriction of irritant foods such as spicy foods, caffeine, and fried foods because it may allow the gastric and duodenal mucosa to heal faster.

H PYLORI INFECTION

H pylori is a gram-negative bacillus described microscopically as spiral- or U-shaped. The prevalence increases with age. By age 18 years, 25% of patients had *H pylori*. (17) The bacteria is transmitted via the fecal-to-oral or oral-to-oral route. Most people are asymptomatic from infection, but the bacteria are also implicated as the cause for some gastric and duodenal ulcers as well as gastric adenocarcinoma and lymphomas. *H pylori* organisms have certain features that contribute to their virulence, including flagella, urease, adhesins, and toxin production. These features allow the organism to overcome the mucosal defenses and cause chronic gastritis, which can eventually lead to ulcer formation. Recently updated guidelines from the 2016 joint European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition discuss testing for *H pylori*. Testing should be directed toward investigation of symptoms and elimination of other causes rather than specifically for diagnosing infection with *H pylori*. This is because patients with functional disease such as irritable bowel syndrome may be chronic carriers of *H pylori* and its treatment in these patients may not necessarily alleviate symptoms. The use of endoscopy for the diagnosis of *H pylori* remains the gold standard of care. At least 6 specimens from antrum and body should be collected for diagnosis. A positive culture alone is sufficient to confirm *H pylori* infection given that its specificity is 100%. Alternatively, a combination of *H pylori*–associated histopathologic findings plus a rapid urease test or a molecular-based test such as polymerase chain reaction or fluorescent in situ hybridization can be used. (18) Noninvasive testing such as urea breath testing and stool antigen testing are recommended for posttreatment testing only. Serology testing is not recommended as part of the evaluation. It is important to note that the use of PPIs and antibiotics can affect the results of *H pylori* testing. (18)

In patients with *H pylori*–associated PUD, eradication therapy should be selected based on susceptibility testing (Fig 1). The guidelines recommend 14 days of therapy and provide standard dosing per weight range (Fig 2). Standardization of dosing is important to ensure eradication.

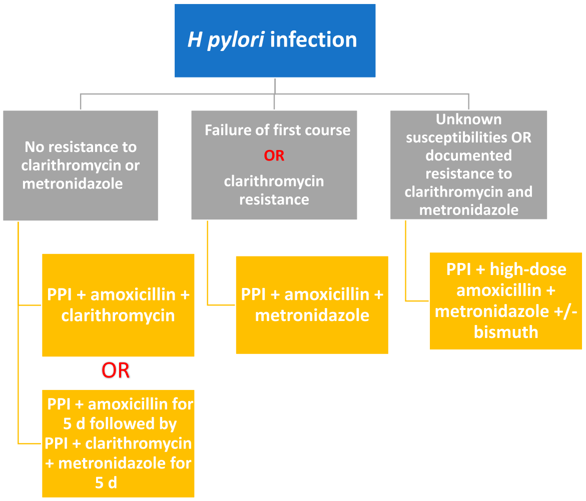
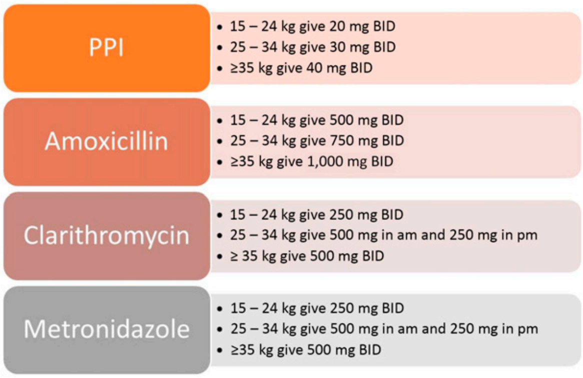

H pylori infection
No resistance to clarithromycin or metronidazole
Failure of first course
OR
clarithromycin resistance
Unknown susceptibilities OR documented resistance to clarithromycin and metronidazole
PPI + amoxicillin + clarithromycin
OR
PPI + amoxicillin for 5 d followed by PPI + clarithromycin + metronidazole for 5 d
PPI + amoxicillin + metronidazole
PPI + high-dose amoxicillin + metronidazole +/- bismuth

Figure 1. Susceptibility-based treatment for *Helicobacter pylori*. (Adapted from Jones NL, Koletzko S, Goodman K, et al; ESPGHAN, NASPGHAN. Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents (update 2016). *J Pediatr Gastroenterol Nutr.* 2017;64(6):991–1003.)
PPI=proton pump inhibitor.



PPI	• 15 – 24 kg give 20 mg BID • 25 – 34 kg give 30 mg BID • ≥35 kg give 40 mg BID
Amoxicillin	• 15 – 24 kg give 500 mg BID • 25 – 34 kg give 750 mg BID • ≥35 kg give 1,000 mg BID
Clarithromycin	• 15 – 24 kg give 250 mg BID • 25 – 34 kg give 500 mg in am and 250 mg in pm • ≥ 35 kg give 500 mg BID
Metronidazole	• 15 – 24 kg give 250 mg BID • 25 – 34 kg give 500 mg in am and 250 mg in pm • ≥35 kg give 500 mg BID

Figure 2. Weight-based doses for *Helicobacter pylori* treatment. BID=twice daily, PPI=proton pump inhibitor.

Weight-based PPI dosing in younger children is higher than in adolescents and adults due to more rapid metabolism. (18) With appropriate treatment, approximately 80% of patients experience resolution of gastric and duodenal ulcers within 4 to 8 weeks. (6)

COMPLICATIONS AND PROGNOSIS

In the pediatric population, PUD could have rare complications such as perforation, hemorrhage, or gastric outlet obstruction. Many patients may present with hematemesis, melena, or symptoms of anemia such as fatigue or syncope. Upper gastrointestinal bleeding is the most common cause of death and the most common indication for surgery. (19) Despite these complications, most patients receiving appropriate treatment will have resolution of gastric and duodenal ulcers within 4 to 8 weeks. (6)

Summary

- The pathophysiology of acid peptic disease relates to an imbalance of acid production and mucosal protective factors.
- The mainstay of treatment of peptic ulcer disease focuses on the use of histamine 2 receptor antagonists and proton pump inhibitors (PPIs).
- Based on some research evidence and consensus guidelines, *Helicobacter pylori* should be treated with a combination of a PPI and antibiotics.
- Based on grade A evidence, initial diagnosis of *H pylori* should be made with positive culture or histopathologic analysis of biopsy samples obtained via endoscopy.

References for this article are at http://pedsinreview.aappublications.org/content/39/11/542.

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1. A 9-year-old girl with persistent abdominal pain was seen multiple times in the clinic with no success in managing her symptoms. She is ultimately referred to a pediatric gastroenterologist for further evaluation. She undergoes an upper endoscopy. The pathology report notes the presence of inflammatory cells and defects in the muscularis mucosa. Based on the pathology report, which of the following is the most likely diagnosis in this patient?
   - A. Celiac disease.
   - B. Gastritis.
   - C. Gastropathy.
   - D. *Helicobacter pylori* infection.
   - E. Peptic ulcer.
2. A 10-year-old boy is seen in the clinic because of diffuse abdominal pain, bloating, and pain immediately after eating for the past 6 to 8 weeks. He wakes up from sleep several times per week with abdominal pain. His mother states that he holds his upper abdomen while he is helping clean up in the kitchen after the meal. He has no history of fever, vomiting, diarrhea, or weight loss. He takes no medications and eats a regular diet. Which of the following is the most likely diagnosis in this patient?
   - A. Appendicitis.
   - B. Gastric ulcer.
   - C. Gastroesophageal reflux.
   - D. Giardiasis.
   - E. Pancreatitis.
3. A 9-month-old boy is brought to the clinic by his parents for evaluation of poor feeding. The parents report that the patient has not been feeding well and seems to have lost some weight. He is very irritable and has been noted to have intermittent vomiting for the past several days. An electrolyte panel shows hypercalcemia, hypophosphatemia, and hyperchloremic acidosis. Which of the following conditions is this presentation most characteristic of?
   - A. Achalasia.
   - B. Hyperparathyroidism.
   - C. Inflammatory bowel disease.
   - D. Intestinal perforation.
   - E. Pyloric stenosis.
4. A 6-year-old girl with mild cerebral palsy was seen 3 months earlier in the clinic because of a new-onset abdominal pain associated with meals. At that time, the patient had a normal complete metabolic panel, complete blood cell count, and urinalysis. Urine culture was negative. She was started on a trial of omeprazole for presumed gastritis. She continued receiving occupational and physical therapy and is progressing nicely. Today she returns to the clinic for follow-up. The parents report that after a short period of improved symptoms, her symptoms recurred, and she complains of abdominal pain and is refusing to eat. Laboratory studies are within normal limits except for anemia on her complete blood count count. There is no history of vomiting, diarrhea, or hematochezia. Which of the following tests is most likely to confirm the diagnosis in this patient?
   - A. Abdominal ultrasonography.
   - B. Serologic testing for *H pylori*.
   - C. Stool antigen testing for *Giardia*.
   - D. Upper endoscopy.
   - E. Urea breath testing.

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5. A 5-year-old girl is brought to the clinic with a history of diffuse abdominal pain that increases several hours after meals for the past few weeks. Her symptoms began around the time she started child care. She was previously diagnosed as having irritable bowel syndrome and was placed on a high-fiber diet. There is no history of vomiting, diarrhea, or constipation. Results of laboratory studies, including complete blood cell count, complete metabolic panel, and urinalysis, are normal. Urine culture is negative. The parents are concerned about peptic ulcer disease associated with *H pylori* because of a positive family history of *H pylori*. Which of the following diagnostic tests will most likely help confirm the diagnosis of *H pylori* in this patient?

   A. pH monitoring.
   B. Serology testing for *H pylori*.
   C. Stool antigen testing for *H pylori*.
   D. Upper endoscopy with biopsies for *H pylori* culture.
   E. Urea breath testing.

Effect of Maternal Substance Abuse on the Fetus, Neonate, and Child

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Practice Gap

Clinicians should be able to describe the short- and long-term effects on the newborn of exposure to substance abuse in utero.

Objectives

After completing this article, readers should be able to:

1. Describe the placental transfer of drugs and their effect on embryogenesis.
2. Identify the methods to screen for drugs in the mother and neonate.
3. Understand the short- and long-term adverse effects of legal and illicit maternal substance abuse in the newborn.
4. Identify therapies for the drug-exposed neonate.
5. Describe American Academy of Pediatrics recommendations for breastfeeding mothers who abuse substances.

INTRODUCTION

The abuse of certain drugs or medications during pregnancy can have detrimental effects on the fetus and neonate. Previous research has shown that 5% of pregnant women use 1 or more addictive substances. (1)(2) Approximately 1 in 20 infants is exposed to illicit drugs. (3) Marijuana, cocaine, heroin, hallucinogens, and inhalants are examples of illicit drugs. (4) According to a 2010 survey conducted by the National Institute on Drug Abuse (NIDA), 16% of pregnant women aged 15 to 17 years, 7.4% of pregnant women aged 18 to 25 years, and 1.9% of pregnant women aged 26 to 44 years abuse illicit substances. (5) From 2002 through 2010, the rate of reported illicit drug use among pregnant women aged 15 to 44 years rose from 3% to 4.4%. (1)(5)(6) The maternal abuse of narcotics has also risen because of "more liberal use of prescription opiates in pregnant women to palliate acute and/or chronic pain." (7) As a result, the incidence of infants born addicted to drugs has increased. (1) The rise in substance use disorders among pregnant women is an alarming public health concern because the abuse of these medications poses a health risk to the fetus, the neonate, and the developing child.

Likewise, maternal abuse of legal substances such as alcohol, caffeine, nicotine, and even nonmedical use of prescription drugs during pregnancy is also

AUTHOR DISCLOSURE Drs Bailey and Diaz-Barbosa have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
ADHD	attention-deficit/hyperactivity disorder
AMPH	amphetamine
CNS	central nervous system
FAS	fetal alcohol syndrome
LBW	low birthweight
MDMA	3,4-methylene-dioxymethamphetamine
METH	methamphetamine
NAS	neonatal abstinence syndrome
NIDA	National Institute on Drug Abuse
PCP	phencyclidine
SSRI	selective serotonin reuptake inhibitor

concerning. Approximately 10% of infants are exposed to alcohol in utero, and 20% are exposed to nicotine. (3) In addition, pregnant women may expose their fetuses to other legal medications (ie, nonsteroidal anti-inflammatory drugs, salicylates, angiotensin-converting enzyme inhibitors, warfarin, and others) that are not known to have abusive potential but that are known to adversely affect the fetus. (3) Thus, "legality of a substance does not necessarily correlate with its safety profile." (4) These substances, whether illicit or licit, can have long-lasting effects beyond the neonatal period. However, the true incidence of maternal abuse of addictive, commonly used, and/or prescribed substances may never be truly known as substance abuse is frequently underreported. (1)

The purpose of this article is to report trends in prenatal substance abuse, to describe how the fetus is affected in utero, to review methods to test for drug abuse in utero, and to describe licit and illicit drugs of abuse during pregnancy. Treatment of exposed neonates will also be reviewed. This article ultimately serves to update current knowledge of short- and long-term outcomes of drug-exposed neonates with the goal of equipping pediatricians to fulfill their role as lifelong health care advocates to babies, children, and young adults.

PLACENTAL TRANSFER OF DRUGS

The human placenta serves to regulate the flow of substances and nutrients from the mother to the fetus. Medications, drugs, and their metabolites can easily enter fetal circulation from the placenta. Some factors that affect this placental transfer depend on the specific drug, the concentrations of the drug in the maternal and fetal circulations, the method and timing of administration, the genetic makeup of both the mother and the fetus, and the co-administration of other drugs. (8)(9) "Other factors important to drug transfer across the placenta include differences between the maternal and fetal osmotic pressures and pH, as well as changes in the uterine or placental blood flow." (8) Cocaine, heroin, nicotine, and marijuana can affect placental blood flow through vasoconstriction. The other factors that regulate placental drug transfer include high lipid solubility, an unionized drug form, low molecular weight (<5000 Da), and low protein binding. (8) The adverse effects of in utero exposure to drugs can lead to abnormalities in breathing, intrauterine growth restriction, and possibly fetal death. A fetal withdrawal syndrome has been reported in which the abrupt cessation of opiates in utero can lead to premature delivery, low birthweight (LBW), and even stillbirth. (9)

MATERNAL DRUG USE AND ITS EFFECTS ON EMBRYOGENESIS

Structural abnormalities or teratogenicity may also result from in utero drug exposure. The timing of drug exposure in utero determines the effect. (8) One possible adverse effect of any abused drug during the first week of pregnancy is miscarriage. The incidence of this complication is unknown because it may be difficult to determine the exact date of conception and exclude other factors that would cause termination of the pregnancy. It is well known that nearly all drugs of abuse have been associated with preterm birth. (3)

The second to eighth weeks of pregnancy compose the period of organogenesis, when drugs can produce structural abnormalities at the cellular level or interfere with growth of the developing fetus. (3)(8) Barbiturates during pregnancy have been noted to cause dysmorphic features. There is evidence for remodeling of vessels in the heart associated with selective serotonin reuptake inhibitor (SSRI) use during pregnancy. Alcohol, for instance, can produce structural abnormalities that lead to fetal alcohol syndrome (FAS). Prenatal alcohol intake can also cause fetal growth restriction. Likewise, heroin, methadone, nicotine, and cocaine have also been implicated in interfering with fetal growth. However, these effects on fetal growth may also be multifactorial because these abused substances are also known to reduce maternal appetite, can affect placental blood flow, and are sometimes used by women in lower socioeconomic groups with limited and disrupted resources. (8)

By the third month of pregnancy, the differentiation of the central nervous system (CNS) begins and is not completed until after birth. Thus, birth is not an end point, but a developmental milestone. (8) Some addictive drugs that are known to affect the developing CNS are opioids, marijuana, cocaine, and methamphetamine (METH). (3) In addition, in utero exposure to many antiepileptic drugs has been shown to increase the risk of cognitive and behavioral impairments in childhood as a result of widespread neuronal apoptosis in the developing brain. (10)

Although the adverse effects of many drugs on a developing fetus are known, sometimes it is difficult for a pregnant mother to abruptly discontinue a drug. Some mothers may depend on medications for medical reasons. Others may depend on medications such as methadone to prevent drug relapse during pregnancy. The safety of both the mother and the fetus must be considered in the decision to discontinue a medication. "Any drug taken during pregnancy must be considered to be potentially harmful to the fetus, and the risk versus the benefits of its use should be assessed carefully." (8)

DIAGNOSING MATERNAL DRUG ABUSE

In 2003, the Child Abuse Prevention and Treatment Act was revised by the US Congress when they passed the Keeping Children and Families Safe Act. (11) This law empowered individual states to implement a plan for newborns exposed to illicit substances. However, "the Act [left] the decision on who should be tested to the healthcare provider." (11) In 2017, the American College of Obstetricians and Gynecologists (ACOG) recommended universal substance abuse screening during the first prenatal visit for all women regardless of ethnicity, socioeconomic background, poor adherence to prenatal care, or previous adverse pregnancy outcome. (12) Routine screening for substance abuse disorders involves having a brief conversation with the patient and using validated screening tools such as questionnaires. (12)

Most hospitals will perform a drug test on a mother and/or her infant for placental abruption, a history of maternal drug use, repeated spontaneous abortions, cerebrovascular accidents, and hypertensive episodes if there is a concern that any parent is under the influence of a substance, if there is a history of absent or inadequate prenatal care, or if there is a clinical concern for drug withdrawal in the neonate. (7) However, the ACOG recommends that drug testing on a mother be performed in compliance with state laws, only after obtaining a patient's consent, and after informing the mother of potential consequences resulting from a positive test result. (12)(13) Several state governments do have policies to prosecute and incarcerate pregnant women with substance use disorders. (13)(14) However, "this approach has no proven benefits to the mother-infant dyad." (14)

Immunoassays "have been used widely for mass drug screening, with positive samples confirmed by more specific techniques, such as high-performance liquid chromatography and gas chromatography–mass spectrometry." (15) Drug testing can be performed on urine, blood, meconium, hair, or umbilical cord blood or tissue samples, but there is no gold standard. (6)(11) Urine is usually the most noninvasive sample to obtain in a newborn and mother. However, urine has its limitations. Urine toxicology may not detect synthetic opioids, some benzodiazepines, and some designer drugs. (12) The clearance of drugs from urine is very rapid, occurring only within hours to several days after consumption. (12)(15) In addition, urine toxicology tests "provide objective evidence of drug use at one point in time and do not enable providers to determine the frequency of use or degree of use." (14) Meconium is formed in the second trimester and is a composite of all substances that reach the fetal circulation. It reflects drug exposure in the last several weeks to months preceding delivery. Meconium drug screening has higher sensitivity compared with urine specimens (11)(15) and is indicative of long-term drug use. Although a negative urine screen taken with a positive meconium screen may reflect previous use of a substance, a positive urine screen with a negative meconium test result may indicate recent drug use that has not had time to accumulate in the meconium. One limitation of meconium drug screening is delayed detection of maternal drug use in babies who are not passing meconium, which is often seen in premature babies and critically ill babies who are not being fed.

Testing of hair samples as a toxicological screening matrix has been around for decades. (15) A positive hair sample in a neonate indicates third trimester use. However, its use is limited in neonates because only a handful of laboratories can process these specimens, and obtaining a sufficient sample may be difficult for some newborns with very little hair. (15) Maternal or neonatal blood collection is also another option. However, the test is invasive and would reflect recent use only. Umbilical cord blood collection was "shown to perform as well as meconium in assessing fetal exposure to various drugs." (16) However, it is not commonly used due to a narrow time frame to collect cord blood and an unsettled time frame of drug use in the mother. Tissue sample collection, ie, neonatal fingernail, is another option. It would indicate fetal exposure from mid-gestation. (15) There has been little published to substantiate this form of testing other than in case reports.

Substances that are commonly tested for in drug screens are metabolites of marijuana, cocaine, sedatives (ie, barbiturates and benzodiazepines), narcotics (ie, opioids), amphetamines (AMPH), and, less commonly, nicotine. Alcohol may not be included on all drug screens because of "low immunoassay sensitivity for ethanol and the agent's short circulation." (15) Health care professionals may rely on maternal self-report or screening tools to detect abuse of nicotine or alcohol in pregnant women. Sometimes, mothers self-report passive exposure to illicit drugs after a drug screen result is positive. "Passive exposure to heavy amounts of second-hand marijuana or crack cocaine smoke in an adult can result in a positive drug test, but low levels typically do not." (11) In addition to objective tests such as drug screening, several semi-objective tools, such as the modified Finnegan Neonatal Abstinence Scoring Tool, are available to assess a neonate's prenatal exposure to opioids. These tools will be addressed in a separate section.

COMMONLY CONSUMED ADDICTIVE SUBSTANCES

Caffeine

One of the most common addictive, but legal, substances consumed during pregnancy is caffeine. It is a naturally occurring stimulant found in many products, such as tea, coffee, sodas, cocoa, and chocolate. "Caffeine has been detected in amniotic fluid, umbilical cord, urine, and plasma of fetuses, which suggests that caffeine is easily transmitted across the placenta." (17) Although considered to be a fairly harmless substance, studies have shown that pregnant women have slower caffeine metabolism compared with nonpregnant women and that fetuses have immature livers that produce a low level of the enzyme necessary for caffeine metabolism. (17) As a result, newborns exposed to caffeine in utero are at risk for jitteriness, bradycardia, emesis, and tachypnea, which can present at birth and last up to 1 week of age. (7) Other adverse effects that have been reported include miscarriage, preterm delivery, and LBW. (17)(18) It is well known that LBW infants are at risk for obesity, diabetes, and hypertension in adulthood according to the Barker hypothesis. Nonetheless, due to the reported adverse outcomes related to caffeine consumption during pregnancy, the ACOG issued a statement in 2010 advocating for moderate caffeine consumption (<200 mg/d) during pregnancy. (18) The ACOG states that "moderate caffeine consumption does not appear to be a major contributing factor in miscarriage or preterm birth and that the relationship of caffeine to growth restriction remains undetermined." (18)

Nicotine

The most commonly abused substance during pregnancy is nicotine. According to the NIDA, 20% of pregnant women continue to smoke throughout pregnancy. (5) More than 7,000 chemicals that are toxic, carcinogenic, and/or teratogenic can be found in cigarette smoke. (4) Just like caffeine, nicotine easily crosses the placenta, which can expose the fetus to nicotine concentrations that are 15% higher than in maternal blood. (3) In addition to maternal use of cigarettes, a fetus can also be exposed to nicotine through second-hand smoke and through nicotine replacement therapies (ie, gum, lozenges, patches, e-cigarettes), which are equally detrimental to the health of the fetus. (4)(19)(20)

Nicotine has been shown to interfere with oxygen delivery, thus affecting growth of the fetus in utero. Dose-dependent LBW and preterm birth has been associated with prenatal exposure to nicotine. (3)(19)(20) Prenatal use of nicotine also places the fetus at risk for intrauterine death. (9) It has also been described as a "neuroteratogen that comprises critical neural pathways in the developing brain." (3) Reports of sporadic congenital anomalies associated with nicotine have shown an increased incidence "of orofacial clefts, neural tube defects, and cryptorchidism, although large-scale studies have no significant increase in gross malformations." (3)

Postnatally, babies heavily exposed to nicotine in utero are at increased risk for poor arousal, irritability and hyperexcitability, hypertonicity, and tremors. (3)(9) Within the first several months of life, nicotine-exposed infants exhibit signs of poorer self-control, more negative affect, distress in response to limitations, and decreased soothability. (4)(9)(21) There is also an association with sudden infant death syndrome with prenatal and postnatal use of tobacco. Long-term, into childhood and even young adulthood, they demonstrate cognitive deficits and a diminished response to auditory stimuli, an effect that can lead to learning and language disabilities, which can cause poor academic achievement in school. (4) "Prenatal nicotine exposure has been consistently associated with lower IQ throughout childhood." (9) Exposed children as young as 6 years of age are at higher risk for attention deficits, depression, anxiety, and conduct disorders. Interestingly, there was no difference in long-term cognitive outcome between babies exposed to tobacco during the entire pregnancy and those exposed only during the first trimester. This finding emphasizes the need for smoking cessation before pregnancy. (4) "Prenatal tobacco exposure appears to increase the likelihood of tobacco use in childhood and early adolescence." (9) In addition, similar to caffeine, prenatal exposure to nicotine increases the risk of adult disease owing to its association with LBW.

Alcohol

The second most common substance of abuse during pregnancy is alcohol. According to the NIDA, females aged 15 to 44 years reported alcohol consumption during pregnancy slightly greater than 15% and binge drinking during pregnancy at a rate of less than 15%. (5) "Binge drinking is defined as drinking 4 or more drinks on the same occasion on at least 1 day in the past 30 days." (1) In addition, "1% of pregnant women report heavy drinking, defined as drinking 1 or more drinks each day." (1) Because there is no safe limit of alcohol intake for pregnant women or for women of reproductive age who are trying to become pregnant, the recommendation by the ACOG is for such women to abstain from alcohol. (22)

Similar to nicotine, alcohol easily crosses the placenta and can be identified in maternal and fetal blood as well as in amniotic fluid. (6) Alcohol is believed to affect the developing fetus during the embryonic and fetal stages of development. (6) It is also hypothesized that alcohol affects vascular tone in the umbilical vessels through decreased placental blood flow, which may predispose the fetus to hypoxia, causing LBW. (6) In addition to LBW, preterm birth is another short-term complication of maternal alcohol use in utero. A neonatal alcohol withdrawal phenomenon has been described as abdominal distention, excessive mouth movements, jitteriness, irritability, seizures, opisthotonus, and reflex abnormalities in newborns exposed to alcohol in utero. (3)(7) Withdrawal from alcohol can occur several hours after delivery. Duration of signs could last up to 18 months of age. (7)

Long-term complications of prenatal alcohol use are encompassed by the well-described but preventable FAS, which is “characterized by specific facial features, growth deficiency, central nervous system abnormalities, behavioral abnormalities, and intellectual disability.” (3) It is estimated that 0.2 to 1.5 infants for every 1,000 live births are affected with FAS. (1)(23) Prenatally alcohol-exposed adolescents and young adults demonstrate learning problems, attention disorders, and cognitive impairments. They are at risk for impulsivity, irritability, inappropriate sexual behavior, criminal activities, depression, and suicidal tendencies. In addition, “prenatal alcohol exposure appears to be a risk factor for alcohol abuse in young adulthood, even after controlling for other relevant covariates.” (8)

Opioids

Patients may be prescribed opioids during pregnancy for chronic pain or addiction, opioid misuse, and an untreated opioid use disorder. (12) Prescription drug abuse of narcotics has become a growing concern that affects people of all ages, socioeconomic classes, and locations in this country. It is estimated that between 2000 and 2009, the incidence of opioid-exposed newborns with withdrawal symptoms, also known as neonatal abstinence syndrome (NAS), increased from 1.2 per 1,000 hospital births per year to 3.39 per 1,000 hospital births per year. (24)(25)(26) Neonates exposed to opioids in utero are at increased risk for LBW, microcephaly, NICU admissions, and a prolonged hospital stay compared with nonexposed babies. (1)(24) The average length of stay for opioid-exposed babies is 17 days, and 23 days for those requiring medication. (27) Prenatal exposure to opioids also significantly increases the risk of preeclampsia, stillbirth, prematurity, and sudden infant death syndrome. (1)(12) An association between prenatal opioid use and congenital malformations such as congenital heart disease, gastroschisis, and spina bifida has been suggested. (1)(4)(28) However, a recent systematic review of case-control and cohort studies on this subject was unable to confirm this claim. (29)

The most common postnatal complication of in utero opioid exposure is the development of withdrawal symptoms, first described in the early 1900s as *congenital morphinism*. (30) By the 1970s, congenital morphinism had been renamed NAS by Dr Loretta Finnegan. (27) “Although other drugs such as benzodiazepines, amphetamines, cocaine, and barbiturates can produce NAS, studies show that it is highest among opioid-exposed babies.” (1) As a result of NAS, neonates experience problems related to the nervous system, respiratory system, gastrointestinal system, and other regulatory systems. (1) On physical examination, these babies may exhibit abnormal tone, temperature instability, poor feeding, poor suck, difficulty sleeping, seizures, inconsolability, sneezing, stuffiness, high-pitched cry, and tachypnea. (9)(31) Signs and symptoms of NAS occur in 50% to 95% of opioid-exposed infants. (1)(27) Most infants will present with symptoms by 2 to 3 days of age. However, the onset of symptoms may be up to 1 to 2 weeks of age. The American Academy of Pediatrics (AAP) recommends that “a neonate born to a mother on an opioid with a short half-life be observed in the hospital for at least 3 days if there are no signs of withdrawal and that an infant born to a mother on an opioid with a long half-life be observed in the hospital for a minimum of 5 to 7 days.” (7)

Currently, the modified Finnegan Neonatal Abstinence Scoring Tool is the most prevalent tool in the United States to assess for opioid withdrawal in a term or near-term neonate with withdrawal symptoms. (7) “Preterm babies are at lower risk for experiencing drug withdrawal and have less severe and/or shorter courses of withdrawal which may be related to CNS immaturity, differences in total drug exposure, or lower fat depots of drug.” (7) This tool assigns a score based on CNS disturbances, vasomotor and respiratory disturbances, and gastrointestinal disturbances that are commonly associated with opioid withdrawal. The neonate is assessed every 3 to 4 hours 30 minutes to 1 hour after a feeding during his or her hospitalization. “Opioid agonist pharmacotherapy is recommended for infants who have modified Finnegan scores above a threshold level.” (3) Treatment of NAS will be further addressed in a separate section.

“At the pre- and elementary school ages, opioid-exposed children show motor and cognitive impairments, inattention, hyperactivity, and increase in attention deficit disorders.” (4) “Prenatal opiate exposure has also been associated with behavioral problems in childhood.” (9) One study found that infants with a diagnosis of NAS are at greater risk for child abuse and for placement in a foster home. (32) Longer-term, there are very little data accounting for performance in adolescents with a diagnosis of NAS at birth. However, 1 Australian study that evaluated children with a diagnosis of NAS in grades 3 through 7 reported poor and deteriorating school performance in this population of children. (33)

MATERNAL ILLICIT SUBSTANCE ABUSE

Hallucinogens

Recent literature is lacking on the effect of phencyclidine (PCP), lysergic acid diethylamide (LSD), and other hallucinogens on the fetus and neonate. The exact incidence of hallucinogen use during pregnancy is unknown. However, research from the 1980s and 1990s suggests that neonates exposed in utero to hallucinogens are at increased risk for microcephaly and alterations in facial features. (3) Neurobehavioral symptoms in PCP-exposed neonates include "decreased attention, high pitched cry, poor visual tracking, tremors, lethargy, nystagmus, poor feeding, and altered reflexes." (3) Longitudinal studies that follow the neurodevelopment of these neonates into childhood are currently not available.

Inhalants

Inhalant abuse (or volatile substance misuse) involves an intentional or occupational overexposure to chemicals and gases such as fuels, solvents, propellants, glues, adhesives, and paint thinners that produce an alcohol-like intoxication. "Inhalants are legal, inexpensive and easy to obtain, all of which may account for the higher abuse potential among younger individuals." (34). The incidence, teratogenic effects, and long-term sequelae of prenatal inhalant exposure remain understudied at this time. However, previous reports suggest that overexposure to inhalants during pregnancy can increase the risks of preeclampsia, spontaneous abortion, fetal malformations, adverse neurodevelopmental outcome in the newborn, and fetal solvent syndrome, which manifests as LBW, microcephaly, facial dysmorphology, and muscle tone abnormalities similar to those occurring in FAS. (35) It is also suggested that infants prenatally exposed to inhalants are at increased risk for an alcohol-like withdrawal phenomenon in the newborn period. (35)

Marijuana

Marijuana remains an illegal substance under federal law. However, with the legalization of marijuana for recreational and/or medicinal purposes in several US states, the increase in its use among pregnant women is a growing concern. Recent statistics have shown that the prevalence of recent marijuana use among pregnant women increased 62% from 2002 through 2014. (36) "Marijuana elicits a sedative-like effect in the mother primarily due to its active ingredient tetrahydrocannabinol (THC) and can remain in the body for up to one month, thus lengthening fetal exposure to the drug." (6) However, "unlike other drugs, the placenta appears to limit fetal exposure to marijuana as fetal marijuana metabolite levels have been documented to be lower than maternal concentrations in animal studies." (6)

Overall, marijuana is the third most commonly abused drug during pregnancy. However, it is the most common illicit drug used during pregnancy. Fetal exposure to marijuana "does not cause clinically important neonatal withdrawal signs, but may have subtle effects on long term neurobehavioral outcomes." (7) Long-term, the IQ of marijuana-exposed children is not affected. However, studies in school-aged children and adolescents "reveal effects of prenatal exposure to marijuana on behavior, cognition, and achievement, but not on language and growth." (6) "At age 10, children who had been exposed to marijuana during the first and third trimester of pregnancy experience more symptoms of depression compared with controls." (9) In addition, prenatal marijuana exposure doubled the risk of marijuana use among 16- to 21-year-olds. (9) Short-term effects of prenatal marijuana exposure are neurobehavioral. Newborns exposed to marijuana can exhibit sleep disturbances, increased startle and tremors, and a high-pitched cry. (3)(4) There is minimal evidence to suggest that marijuana in utero causes prematurity, LBW, or congenital anomalies. The harmful effects of marijuana on the fetus are related to actions on the developing brain of the fetus, altered uterine blood flow, and altered maternal health behaviors. (3)(6)

Cocaine

Overall, cocaine is the fourth most common substance abused during pregnancy. Cocaine abuse affects at least 750,000 pregnancies per year. (37) Cocaine has sympathomimetic properties that can cause vasoconstriction, hypertension, tachycardia, and cardiac arrhythmias. As a result, cocaine use during pregnancy increases the risk of placental abruption, abortion, and premature birth, among other complications. As with any other substance, the most dangerous period of drug use is during organogenesis. (37) An increased risk of congenital malformations, especially of the brain and heart, has been suggested. Fetal brain growth, weight, and length are also restricted secondary to the vasoconstrictive effects of the drug. In addition, the fetus is also at risk for bowel infarction, atresia or perforations, porencephalic cysts, and nonsyndromic limb malformations. (37)

In the cocaine-exposed neonate, restricted fetal growth leads to LBW, microcephaly, and decreased length. (9)(38) Signs and symptoms of prenatal cocaine exposure manifest within the first 2 to 3 days of life. These symptoms include hyperalertness, excessive suck, jitteriness, high-pitched cry, irritability, and autonomic instability (ie, tachycardia, hypertension). (3)(38) Delivery room resuscitation, intubation, and NICU admissions occurred more frequently in cocaine-exposed babies. (38)

Long-term, "growth restriction among prenatal cocaine exposure children has been documented to continue past infancy and may persist in children up to 10 years of age."

(4) Although, recent studies have shown that children exposed to heavy cocaine in utero are at increased risk for higher body mass index and blood pressures compared with nonexposed children. (37) Although IQ is not necessarily affected, executive functions such as cognition, language skills, memory, problem-solving skills, attention, and behavior are affected. Exposed children were more likely to be in the custody of child protective services, a foster parent, or an adoptive parent. Little is known about the long-term adult health effects associated with in utero cocaine exposure. (37)

METH AND ITS METABOLITES

METH is "a member of a group of sympathomimetic drugs that stimulate the CNS." (6) 3,4-Methylenedioxymethamphetamine (MDMA) and AMPH are metabolites of METH. "According to the United Nations, 1.3% of the general population in Central and North America use amphetamine-type stimulants." (4) METH "readily passes through the placenta and blood-brain barrier and can have significant effects on the fetus and newborn." (6) One multicenter prospective longitudinal study on METH-exposed neonates suggested that prenatal METH use is associated with LBW. (39) Microcephaly and decreased length have also been associated with prenatal METH use, whereas other studies have demonstrated that when taken at therapeutic doses, METH has not been shown to have negative effects on the fetus or neonate. (9) Similar to cocaine, there is an increased risk of prematurity, placental abruption, (39)(40) and congenital malformations of the brain and heart. (4)(7) Unlike cocaine, METH-exposed newborns exhibit minimal symptoms, if any. Long-term, short stature and deficits in fine motor performance may exist during the first 3 years of life. (4)(7) At 3 and 5 years of age, METH-exposed babies are at risk for behavioral problems, depression, and attention-deficit/hyperactivity disorder (ADHD). (41) At almost 8 years of age, prenatal METH exposure is associated with increased cognitive delays. (42)

AMPH, also known as *speed*, is used either legally for the treatment of ADHD or for recreational purposes. It is not known how many women are using AMPH either legally or illegally during pregnancy. AMPH is not known to be teratogenic. (4) However, it is associated with a higher odds of prematurity and LBW. (4) Long-term, "it has been reported that AMPH causes an increased prevalence of ADHD, aggression, and learning difficulties attributed to attention, memory, and motivation deficits." (4)

MDMA, also known as *ecstasy,* "is a derivative of AMPH that has both stimulant and hallucinogenic properties." (4) It releases serotonin, norepinephrine, and dopamine. (4) Very little is known about the prevalence of MDMA use during pregnancy. However, an increased risk of cardiovascular and musculoskeletal anomalies in MDMA-exposed fetuses has been reported. (4)

PRESCRIBED AND OVER-THE-COUNTER MEDICATIONS

Selective Serotonin Reuptake Inhibitors

The SSRIs (eg, Prozac, Zoloft, Celexa, Lexapro) are a class of antidepressant medications that became available in 1988. (7) In the past few decades, the use of SSRIs has increased due to the increasing incidence of depression. "Women have a strong disposition to depression: 10-20% of women will present with a major depressive disorder during pregnancy and the immediate postpartum period and 5 to 13% of pregnant women will be treated with an SSRI." (43)(44) "Treatment of maternal depression during pregnancy and afterwards at the lowest effective dose is uniformly recommended despite the potential side effects to the fetus and newborn." (7)(44)

The SSRIs have been shown to cross the placenta, and SSRI use, especially during the third trimester, has been shown to increase the risk of an SSRI withdrawal-like syndrome in the newborn that consists of temperature instability, irritability, tremors, poor suck, poor feeding, hypertonia, respiratory distress, seizures, and sleep disturbances, among other symptoms. (7)(44)(45) Neonatal adverse effects are more commonly reported with the prenatal use of paroxetine and fluoxetine and represent the effects of cholinergic and serotonin-induced manifestations of the drug, which regulate cardiovascular, respiratory, and brain functions. (43)(44) These signs occur in 30% of SSRI-exposed neonates and can present within hours to days after delivery and can persist up to 2 to 4 weeks of age consistent with the decline in the serotonin levels of the neonate. (44) Use of SSRIs during late gestation has also been reported to increase the risk of persistent pulmonary hypertension of the newborn (PPHN) by 2- to 6-fold. (44)(45) It is suggested that the persistent pulmonary hypertension of the newborn is secondary to the potent pulmonary vasoconstrictive effects of serotonin. (44) Primary pulmonary hypertension has also been seen in adults with elevated serotonin levels. (44) These adverse effects can increase the risk of NICU admission for the SSRI-exposed neonate. "With respect to teratogenicity, studies vary in quality and design" and present conflicting findings. (45) Most "prospective studies and meta-analyses suggest no increased risk of teratogenicity and SSRI use while studies demonstrating teratogenicity are primarily retrospective and case control in nature, with their inherent limitations." (45)

SEDATIVES (BARBITURATES AND BENZODIAZEPINES)

Barbiturates (ie, phenobarbital) “are classified as sedative/hypnotics because of their CNS depressant and sleep-inducing effects.” (46) When prescribed, barbiturates are used as anesthetic and anticonvulsant agents. As with any drug, barbiturate use can be addictive. “The abuse of barbiturates, both licit and illicit, peaked in the early 1970s and declined by the mid 1980s when the treatment of anxiety and insomnia was accomplished with much safer drugs like benzodiazepines.” (46) As a result, recent literature is lacking with respect to short- and long-term outcomes of barbiturate-exposed newborns.

Barbiturates freely cross the placenta. (46) “Neonates exposed to barbiturates in utero, especially during the third trimester, can experience an abstinence syndrome similar to NAS.” (46) The withdrawal symptoms in barbiturate-exposed babies also tend to begin closer to a week after birth and can last up to 1 month of age. There are some reports of LBW (11) and congenital malformations (ie, neural tube defects, cleft lips and palates, cardiac defects, and microcephaly) in this population of patients. (8)(47) In utero barbiturate use, particularly phenobarbital, may potentially predispose the fetus or newborn to bleeding complications by increasing the rate of oxidative degradation of vitamin K. (48)

Benzodiazepines are commonly prescribed for their sedative effects. Similar to barbiturates, recent literature on the short- and long-term effects of in utero benzodiazepine exposure is sparse. However, it has been shown that benzodiazepines cross the placenta and can accumulate in the fetus. (3) Previous studies have reported signs of benzodiazepine withdrawal in exposed newborns that include hypoventilation, hypertonicity, irritability, and “floppy infant syndrome,” particularly after use in late gestation. (3) “These symptoms can appear within a few days to 3 weeks after birth and can last for several months.” (3) It has also been previously reported that benzodiazepines increase the risk of preterm birth and LBW. (3) However, there has been no consistent evidence linking this class of drug with congenital anomalies.

TREATMENT OF THE DRUG-EXPOSED NEONATE

Treatment of the drug-exposed neonate often begins with treating the mother. Pregnant women and women of childbearing age should be counseled about the harmful effects of all medications. (12) These women should also be provided support and additional resources to aid them in discontinuing the medication as early as possible. A “public health response” has been initiated by the AAP to promote primary prevention of drug abuse, particularly opioid use, during pregnancy. (14) However, realistically, this is not always possible. For instance, for pregnant women who are already abusing opioids, it is not possible to counsel these women to abruptly discontinue these medications. Instead, they may be prescribed agonist therapy at the most effective dose to stabilize maternal and fetal withdrawal symptoms, reduce cravings for heroin, increase attendance at prenatal care clinics, and promote other positive maternal health behaviors. (4)(9)(14) Since the late 1970s, methadone has been the drug of choice in pregnant women addicted to opioids. Buprenorphine is a more recent alternative to methadone that has been shown to have minimal to mild withdrawal symptoms in the exposed neonate, shorter treatment durations for NAS, and decreased length of hospital stay for the newborn. (6)(7)(25) To date, there has been no consistent evidence to show a relationship between the maternal agonist therapy dose and the severity of NAS. (12)(49)

Maternal opioid maintenance therapies are not without substantial risk as neonatal withdrawal from illicit or prescribed opiates can incite NAS. Nonpharmacologic care is the initial treatment option for NAS. (30) Nonpharmacologic treatment would include providing swaddling, comfort, and a quiet space for the neonate, with minimal overstimulation by light, noise, or handling. (44) If the newborn fails nonpharmacologic measures or the newborn’s Finnegan scores reach a threshold level, then pharmacologic treatment would be initiated with 1 of the following regimens: 1) morphine with or without phenobarbital, 2) diluted tincture of opium, 3) methadone with or without clonidine, or 4) the newest option, sublingual buprenorphine. (4)(50) However, tincture of opium is rarely used for NAS therapy due to the need to dilute the medication, thus creating the potential for medication error. (23) “Little empirically based evidence supports the use of one regimen over the other, reflecting a paucity of randomized studies in this area.” (3) Evidence suggests that using a standardized protocol for pharmacologic treatment of NAS is more important than the choice of regimen in decreasing treatment days and hospital stays in the exposed newborn. (27)

Most newborns exposed to other substances that can produce withdrawal-like symptoms, such as SSRIs, marijuana, cocaine, nicotine, alcohol, antidepressants, and antipsychotics, do not reach cutoff values for pharmacologic treatment as determined by the Finnegan scoring system. (3) Unlike neonatal opioid withdrawal, generally there are no specific pharmacologic treatments for non–opioid-exposed infants. (3)(37) The non–opioid-exposed neonate is treated based on symptoms, which may require medications or nonpharmacologic treatments. Long-term, all drug-exposed babies benefit from early intervention services to identify and treat areas of delay in child development. (27)(33)

BREASTFEEDING AND MATERNAL DRUG USE

"Some of the well-known advantages of breastfeeding are the transfer of maternal immunity to the newborn, increase in mother-infant bonding, enhancement of maternal confidence, and active maternal participation in the management of the infant." (30) In the case where a breastfeeding mother is also a substance user, there is some hesitation to encourage breastfeeding because of the possible secretion of these drugs into human milk. "Maternal substance abuse is *not* a categorical contraindication to breastfeeding." (51) However, it is contraindicated if the mother is using illicit drugs such as PCP, cocaine, or marijuana. (51) The AAP recommends that mothers minimize their intake of alcohol when breastfeeding. Their recommendations have been previously published. (51) The AAP also strongly discourages the use of nicotine but states that it is not an absolute contraindication to breastfeeding. (51)

FUTURE DIRECTIONS

Despite the abundance of literature published on the topic of the drug-exposed fetus and neonate, there are still gaps and inconsistencies in knowledge. For instance, "attempts to attribute effects to a specific drug exposure have often been confounded by the use of multiple drugs and limited access to a large diverse population." (38) Long-term outcomes for many drugs of abuse during pregnancy still need investigation beyond the immediate newborn period into childhood, adolescence, and even young adulthood. Optimal strategies for diagnosing drug abuse in utero, for diagnosing withdrawal symptoms, and for treating a symptomatic newborn are still being elucidated. In an era where health care costs are of utmost importance, further research should relate optimal treatment strategies with cost to administer these treatments. In addition, amid the legalization of marijuana in several states and the growing opioid crisis, physicians will have to gain more insight into how to deal with these legal and medical dilemmas to optimize patient care.

CONCLUSION

Maternal substance abuse during pregnancy is an increasing problem in our society that has adverse perinatal and neonatal outcomes. Licit and illicit drug use during pregnancy can have equally detrimental effects on the newborn. Drug-exposed newborns are more likely to be LBW, preterm, and microcephalic; to require delivery room resuscitation and NICU admission; and to have longer hospital stays compared with nonexposed neonates. Primary prevention of maternal drug abuse is optimal, but not always possible. Health care professionals need to become increasingly aware of the signs and symptoms of neonatal drug withdrawal and how to mitigate these symptoms in the newborn period. We should also strive to advocate for these babies beyond the newborn period. Further research and support programs are needed to improve the short- and long-term outcomes and development of the drug-exposed neonate.

Summary

- On the basis of observational studies, babies born to mothers who abuse legal substances such as alcohol and nicotine are at increased risk for low birthweight (LBW), developmental disabilities, and long-term behavioral problems. (3)(4)(6)(9)
- On the basis of observational studies, babies born to mothers who abuse narcotics (ie, opioids) are at increased risk for microcephaly, LBW, admission to the NICU and prolonged hospital stay due to withdrawal symptoms, and long-term cognitive and behavioral impairments. (1)(4)(24)
- On the basis of observational studies, babies born to mothers who abuse illegal substances such as phencyclidine (PCP), marijuana, amphetamines, and cocaine are at increased risk for microcephaly, LBW, abnormal neurobehavioral symptoms, and long-term cognitive delays. (3)(4)(6)(7)(9)(38)
- On the basis of observational studies, babies born to mothers who take prescription or over-the-counter medications such as selective serotonin reuptake inhibitors and sedatives are primarily at risk for persistent pulmonary hypertension of the newborn and withdrawal-like symptoms in the newborn period, respectively. (3)(44)(45)(46)
- On the basis of observational studies, the initial treatment of symptomatic neonates born to mothers who abuse illegal or legal substances involves nonpharmacologic care such as swaddling and comforting the baby. If the baby fails nonpharmacologic therapy, then pharmacologic treatment with medications such as opioids or clonidine may be indicated, especially in opioid-exposed newborns. (4)(30)(44)(50)
- On the basis of observational studies, all babies born to mothers who abuse licit or illicit substances during pregnancy would benefit from long-term developmental follow-up and early intervention services. (27)(33)
- On the basis of expert opinion, breastfeeding mothers who abuse cocaine, marijuana, and hallucinogens (ie, PCP) should abstain from breastfeeding their newborns. (51)

References for this article are at http://pedsinreview.aappublications.org/content/39/11/550.

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1. A newborn boy is admitted to the newborn nursery. He was born to a mother with polysubstance abuse during pregnancy. As you take the pregnancy history, you consider which substances were most likely to have transferred to the fetus by placental drug transfer. Which of the following factors would increase placental drug transfer from the mother to the fetus?
   - A. High lipid solubility.
   - B. High molecular weight.
   - C. High protein binding.
   - D. Ionized drug form.
   - E. Vasoconstriction.
2. A clinician caring for a group of babies in the special care nursery is notified by the hospital laboratory that a meconium drug screen has returned positive on 1 of the newborns. Meconium drug screening indicates which of the following time frames of drug exposure of this newborn infant before delivery?
   - A. Days to 2 weeks before delivery.
   - B. In the first trimester of gestation.
   - C. Several hours to a few days before delivery.
   - D. Several weeks to months preceding delivery.
   - E. Within 24 hours before delivery.
3. You are speaking to a group of prospective young primigravida mothers who are early in their pregnancy. The discussion centers around having a healthy pregnancy and delivery. In addition to prenatal care and the importance of prenatal vitamins, you discuss avoiding substances of abuse. Which of the following is the overall most commonly abused substance during pregnancy?
   - A. Alcohol.
   - B. Cocaine.
   - C. Marijuana.
   - D. Nicotine.
   - E. Opioids.
4. You are caring for a 2-day-old full-term newborn in the well-baby nursery. The baby is manifesting temperature instability, irritability, tremors, poor feeding, and sleep disturbance. Review of the medical records reveals maternal use of selective serotonin reuptake inhibitors (SSRIs) in the third trimester, raising the possibility of these signs as a result of SSRI withdrawal-like syndrome. Which of the following represents the approximate percentage of neonates exposed to SSRIs that will manifest signs of possible SSRI withdrawal?
   - A. <5%.
   - B. 10%.
   - C. 30%.
   - D. 60%.
   - E. >90%.
5. A newborn baby boy with neonatal abstinence syndrome (NAS) was admitted to the newborn nursery for management. Which of the following is the most appropriate initial treatment option for NAS in this patient?
   - A. Diluted tincture of opium.
   - B. Methadone with or without clonidine.
   - C. Morphine with or without phenobarbital.
   - D. Sublingual buprenorphine.
   - E. Swaddling, comfort, and minimal overstimulation.

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Index of Suspicion

1 Hematemesis in a 30-month-old Boy

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EDITOR'S NOTE
We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Drs Damodharan and Danko have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 30-month-old boy with no significant medical history presents to the emergency department with a single unprovoked episode of hematemesis. The mother describes the emesis as bright red blood. This has never occurred before, and after the episode the patient was drinking milk with no noticeable pain or irritation. The mother reports that for a few days preceding the hematemesis the patient's solid intake decreased, but he continued to take in liquids without difficulty and had no weight loss. She also noted dark maroon–colored stools for about the past week. He is not taking any medications and is otherwise healthy.

Vital signs are all within normal limits for his age. On physical examination, the patient appears pale but has no abdominal tenderness, hepatomegaly, splenomegaly, lesions in the oropharynx, or petechiae and bruising on the skin.

A complete blood cell count is obtained and is significant for a hemoglobin level of 10.6 g/dL (106 g/L), which is down from 12.0 g/dL (120 g/L) from a lead screening a few weeks earlier. A stool guaiac sample is also obtained and is positive.

The decision is made to admit the patient to the pediatric gastroenterology service for further endoscopic evaluation. On admission, the patient continues to have multiple blood-tinged emesis episodes and refuses to take in solids. During these episodes, his vital signs remain within normal limits and he continues to tolerate oral intake of fluids.

He is made nothing per os overnight and is taken for esophagogastroduodenoscopy in the morning for presumptive upper gastrointestinal (GI) bleed given his history of hematemesis and melena. Endoscopic evaluation reveals a bleeding Dieulafoy lesion in the proximal gastric body (Fig 1). The mucosa surrounding the lesion is injected with epinephrine to provide hemostasis, and the vessel is then electrocoagulated with a bipolar probe (Fig 2). The patient tolerates the procedure well.

The next day the patient has 1 more episode of coffee ground emesis, but a repeated complete blood cell count shows a hemoglobin level increase to 11.2 g/dL (112 g/L). He is discharged after tolerating his normal diet with no more episodes of vomiting.

DISCUSSION

The Condition

Dieulafoy lesions are an uncommon cause of GI bleeds in not only the pediatric population but in adults as well. The term refers to a large tortuous artery in the submucosal layer that erodes to the surface. The lesion usually occurs in the proximal stomach, but it can be found in the small bowel, colon, and esophagus.

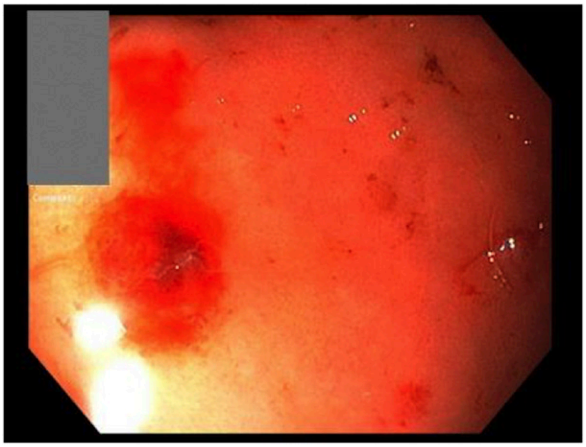

Figure 1. Bleeding Dieulafoy lesion in the gastric body.

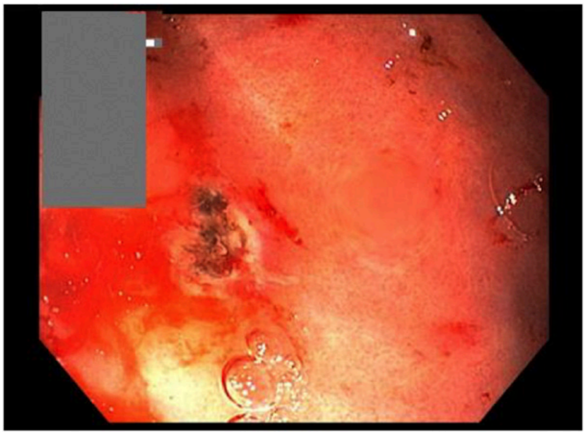

Figure 2. Dieulafoy lesion after obtaining endoscopic hemostasis.

The etiology of the lesion is unclear, but it seems to be a histologically normal artery that fails to undergo normal branching as it traverses the GI wall. It is postulated that the relatively large pulsating vessel disrupts the epithelium and subsequently erodes, causing massive hemorrhage. The lesion does not cause symptoms until it bleeds, so its true incidence is unknown. However, these lesions are believed to account for 1% to 2% of all acute GI hemorrhages in adults. (1) Only a handful of case reports have shown Dieulafoy lesions in the pediatric population, with little information known of its incidence.

Differential Diagnosis

Upper GI bleeding typically presents with hematemesis, melena, and, in some patients, hematochezia. The differential diagnosis in our patient's age group primarily includes esophagitis, gastritis, peptic ulcer disease, Mallory-Weiss tears, esophageal varices, vascular malformations, and foreign bodies. The initial evaluation should be directed at assessment of the risk of circulatory compromise. After this, a thorough history and physical examination should be performed to narrow the differential diagnosis. A history of gastroesophageal reflux, repeated vomiting, and abdominal pain raises the suspicion of esophagitis, gastritis, peptic ulcer, or a Mallory-Weiss tear. A history of jaundice, or findings of splenomegaly or a firm nodular liver edge, suggests underlying liver disease and bleeding from esophageal varices secondary to portal hypertension. When considering liver cirrhosis, it is important to realize that the liver may be enlarged, shrunken, or normal in size depending on the stage of the disease. It is also important to consider extra-GI causes that can present as GI bleeds. For example, recurrent epistaxis may point to a nasopharyngeal source. Patients with thrombocytopenia or a coagulopathy would be at risk for bleeding from a preexisting lesion in the GI tract. A thorough drug history must be taken, including over-the-counter medications such as nonsteroidal anti-inflammatory drugs. The skin should also be examined for any evidence of vascular malformations that can be associated with GI vascular disorders. Initial laboratory evaluation may include a complete blood cell count with a differential count, a complete metabolic panel, and coagulation studies. Plain films can be obtained to look for evidence of bowel obstruction or foreign bodies, and ultrasonography can assess for liver disease. A nasogastric aspirate may also be helpful to confirm active gastric bleeding. However, the definitive test is endoscopy, which is both diagnostic and potentially therapeutic.

Treatment

The initial treatment of choice for most Dieulafoy lesions is endoscopic management. As in our patient, epinephrine is typically injected to achieve hemostasis, which is then followed by electrocoagulation. Other endoscopic therapies include sclerotherapy, hemostatic clipping of the ulcerated lesion, and band ligation. (2) Of note, patients diagnosed as having a Dieulafoy lesion are at risk for recurrent bleeds even after successful endoscopic treatment. For lesions that fail to respond to endoscopic management, angiography with embolization has been used as a second-line treatment, with surgery performed as a last option. (2)

Lessons for the Clinician

- Dieulafoy lesions are rare but should be considered in patients who present with signs of an upper gastrointestinal bleed.
- For patients who present with gastrointestinal bleeding in hemodynamic decline, stabilization and prompt endoscopic evaluation and therapy are indicated to prevent further deterioration.
- Patients typically recover quickly after successful treatment of a Dieulafoy lesion but should always be aware of the risk of a repeated bleed.

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2 Epigastric Pain in a 14-year-old Boy

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AUTHOR DISCLOSURE Drs Berlin, Weisgerber, and Loconto have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 14-year-old boy with a medical history significant for mild intermittent asthma presents to the emergency department with 5 days of epigastric pain, chest pain, poor oral intake, and subjective fevers. On initial presentation he is diagnosed as having viral gastritis and is sent home from the emergency department with an antiemetic drug and instructions for supportive care. However, his symptoms worsen and he is referred back to the emergency department by his primary care physician, ultimately resulting in his admission. The patient is afebrile on presentation, with age-appropriate vital signs. Physical examination findings are normal except for discomfort with deep palpation of his epigastric region. Results of initial evaluation (including abdominal radiography, blood cell count, electrolyte levels, liver function testing, lipase levels, and urinalysis) are within normal limits. Therefore, the initial concern is for a combination of gastritis and constipation: he is treated symptomatically without improvement.

As symptoms persist, he is unable to tolerate any oral intake due to pain and eventually requires placement of a nasogastric tube to maintain proper nutrition. He notes that his most prominent pain localizes to the substernal region. In addition, he begins complaining of odynophagia. A thorough review of the patient's history reveals an isolated episode of food impaction approximately 1 year earlier and a father with significant gastroesophageal reflux disease complicated by an esophageal stricture at age 20 years. The patient remains afebrile, with repeated laboratory work and imaging findings within normal limits.

Given odynophagia and substernal chest pain, the differential diagnosis shifts toward an esophageal pathology, although the differential diagnosis for his suspected esophagitis remains large. A family history of esophagitis and a personal history of food impaction are commonly reported with eosinophilic esophagitis (EoE). However, the acute onset of his condition with reported fever suggests possible infectious etiologies, such as *Candida albicans* and herpes simplex virus (HSV). Finally, significant gastroesophageal reflux disease (GERD) resulting in erosive esophagitis is considered. Pill esophagitis and other etiologies of corrosive esophagitis are also considered, but the patient denies any such ingestion.

Direct visualization with biopsy is required. Gastroenterology is consulted, and the boy undergoes endoscopy, which reveals significant ulceration of the lower esophagus. At this point, concern for EoE is so significant that he is given intraprocedural intravenous methylprednisolone and is immediately started on daily oral fluticasone as presumptive treatment for EoE. Additional testing reveals the true diagnosis.

DISCUSSION

The biopsies taken during endoscopy show substantial neutrophilic inflammation, with only 0 to 2 eosinophils noted per field, effectively ruling out EoE. Corticosteroids are immediately stopped, and the dose of his proton pump inhibitor is increased, as GERD becomes the most likely diagnosis. After 2 days, testing and culture for HSV returns positive, confirming the diagnosis of HSV esophagitis.

Clinical Course and Management

The patient is started on acyclovir therapy (800 mg 3 times daily) and has improvement in symptoms. He is discharged from the hospital with 10 days of acyclovir and a nasogastric tube in place to facilitate feeding. He improves substantially on this regimen, and tube feedings are quickly discontinued as his odynophagia resolves. He follows up with gastroenterology 4 weeks after discharge; at this time he denies any odynophagia or chest pain, and his weight loss has resolved.

The Condition

Herpes simplex virus esophagitis is increasingly becoming recognized as an etiology of infectious esophagitis in both immunocompetent and immunosuppressed individuals. Most commonly, this disease process occurs with the primary infection of HSV in a host. Generally, there is local spread of HSV from an orolabial or pharyngeal source directly to the esophagus. This was likely the case in the present patient, as he had been sharing drinks with his mother—who had an open cold sore—about a week before his admission.

Herpes simplex virus type 1 is the most common cause, although HSV2 has been implicated. Previous research has suggested that the disease process is more likely to occur in the presence of esophageal pathology (such as severe GERD or biopsy sites) as the virus is more likely to infect traumatized tissue, although there are many cases—including our patient—where there is no identified damage to the mucosal integrity.

Typically, HSV esophagitis presents with acute odynophagia and retrosternal chest pain, as in this patient. The classic patient is an otherwise healthy male younger than 40 years. Oropharyngeal or genital ulcers are generally absent (reported to be present in less than one-quarter of cases). Many patients report a similar prodrome of fever and malaise but can also report respiratory symptoms or sore throat.

Endoscopy is required for diagnosis and should reveal ulcerated lesions in the distal one-third of the esophagus. Biopsy should be performed, preferably at the ulcer edge. Pathologic examination can show a neutrophilic inflammation, eosinophilic intranuclear inclusions, or multinucleated giant cells. Polymerase chain reaction and culture should confirm the diagnosis of HSV esophagitis.

Differential Diagnosis

The differential diagnosis for esophagitis can be separated into 3 broad categories: infectious, eosinophilic, and erosive. Erosive esophagitis includes pill esophagitis and erosive esophagitis secondary to GERD. There is a multitude of medications associated with pill esophagitis, including medications that change the tone of the lower esophageal sphincter (such as opioids or anesthetics) or pills that cause direct mucosal injury, such as nonsteroidal anti-inflammatory agents, potassium chloride, or ferrous sulfate. Eosinophilic esophagitis is characterized by mucosal inflammation secondary to eosinophilic infiltration of esophageal squamous mucosa. The classic patient presenting with EoE is one with a history of atopy (including asthma, such as in our patient) and a history of food impaction. Typically, patients will also have a family history of either EoE or significant GERD. Given the patient's presentation, EoE was very high on our differential diagnosis list. However, biopsy would show many eosinophils per high-power field in the case of EoE.

Infectious esophagitis can be secondary to fungal pathogens (most commonly *Candida*), viruses, or bacteria. The most common infectious etiologies are *C albicans*, HSV, and cytomegalovirus. *Candida* esophagitis can be seen in either immunocompetent or immunocompromised hosts and presents with multiple white plaques in the esophagus. Cytomegalovirus esophagitis is seen almost entirely in immunocompromised patients. Finally, HSV esophagitis can be seen in either immunocompromised or immunocompetent patients but is much more likely in the immunocompromised patient.

Treatment and Prognosis

In immunocompetent patients, HSV esophagitis is typically a self-limited disease. Acyclovir should be offered to all patients because it may speed recovery, although the true benefit of antiviral therapy is unknown at this time. Supportive care, including good nutrition, is important. Finally, all patients should have underlying immune conditions (specifically human immunodeficiency virus) ruled out because this condition is still much more common in those with immunodeficiency.

Lessons for the Clinician

- Consider esophageal pathology early in a patient presenting with odynophagia and chest pain.
- Herpes simplex virus esophagitis can occur in immunocompetent hosts and should be considered in the differential diagnosis of esophagitis.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/39/11/562.

Suggested Readings

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3 Recurrent Symptom of Sleepiness in an Adolescent Girl

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PRESENTATION

A 17-year-old girl presents with recurrent episodes of sleepiness. Her mother brought her to the emergency department after she was difficult to awaken from sleep. She has had recurrent symptoms of fatigue, difficult arousability, tremulousness, and diaphoresis for 5 months and experiences mild symptoms daily, which are alleviated by eating. In addition, she has had recent weight loss of 4 lb (1.8 kg), headache, and irregular menstruation. The remainder of her medical and family history is normal.

On hospital admission her vital signs are normal. Growth parameters include weight of 103.4 lb (46.9 kg), height of 60 in (152 cm), and BMI of 20.3 (BMI *Z*-score, –0.3); physical examination findings are normal, and no unusual skin findings are seen. Her initial serum glucose level is 24 mg/dL (1.33 mmol/L), and dextrose-containing intravenous fluids are started. Pediatric endocrinology is consulted to aid in investigation and management.

On further questioning, she reports a previous evaluation in another hospital for these episodes. During her admission she is found to have a fingerstick glucose level of 21 mg/dL (1.17 mmol/L) and receives 2 ampules of dextrose 50% due to recurrent hypoglycemia. She is admitted to the PICU for further monitoring. During a hypoglycemic event, her serum glucose level was 41 mg/dL (2.28 mmol/L), β-hydroxybutyrate level, 2.1 mg/dL; C-peptide level, 3.6 ng/mL; and serum insulin level, 16.6 μIU/mL (115.29 pmol/L) (Table). Because of recurrent unprovoked hypoglycemic episodes, a fasting study is not performed. Other laboratory tests at the time of hypoglycemia show normal levels of cortisol, free fatty acids, growth hormone, lactic acid, and pyruvate. In addition, magnetic resonance imaging (MRI) of the abdomen reveals a 10-mm nodule in the head of the pancreas. She is prescribed diazoxide 50 mg 3 times daily and is discharged from the hospital. She tolerates the medication well at home without hypertrichosis or fluid retention, but she continues to have frequent hypoglycemic episodes. In addition, she is noncompliant with home glucose checks, checking only when severely symptomatic. Further testing reveals the diagnosis.

AUTHOR DISCLOSURE Drs Lambuth, Lantigua, Evangelista, Tchakarov, and Shah have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE. **Timeline of Events in the Emergency Department**

			INTERVENTION				INTERVENTION					INTERVENTION				
Fingerstick glucose, mg/dL	21	→	One ampule dextrose 50%	→	60	→	One ampule dextrose 50%	→	53	40	→	Intravenous fluids dextrose 5% in 0.45% normal sodium started	→	160	51	37
Serum glucose, mg/dL										41						
Insulin, μIU/mL Reference range, 2.6-24.9 μIU/mL										16.6						
C-peptide, ng/mL Reference range, 1.1-4.4 ng/mL										3.6						
β-hydroxybutyrate, mg/dL Reference range, 0.2-2 mg/dL										2.1						

DISCUSSION

Given her history of pancreatic head mass and hypoglycemic episodes, insulinoma was strongly suspected. Her previous evaluation showed normal insulin levels, inappropriate in the setting of hypoglycemia. During her second hospitalization, she was intermittently hypoglycemic despite a conservative wean of dextrose-containing fluids, good oral intake, and an increased dose of diazoxide. Calcium levels were normal, reassuring against the presence of parathyroid pathology, which would be concerning for multiple endocrine neoplasia type 1 (MEN1) syndrome. Her physical examination lacked features concerning for tuberous sclerosis or neurofibromatosis. In addition, follicle-stimulating hormone, luteinizing hormone, estradiol, thyrotropin, free thyroxine, prolactin, corticotropin, and insulinlike growth factor-1 levels are appropriate.

Previous MRI showed a discrete lesion in the head of the pancreas (Fig 1). A computed tomographic (CT) scan focusing on the pancreatic area showed an ill-defined nodule in close proximity to the common bile duct and anterior surface of the inferior vena cava. Endoscopic ultrasonography paired with fine-needle aspiration showed a similar lesion corresponding to the location seen on CT. Fine-needle aspiration performed during endoscopy revealed tumor cells consistent with insulinoma. Pediatric surgery was consulted, and an enucleation of the pancreatic tumor was performed. Further histologic examination of tissues obtained revealed a low-grade, well-differentiated neuroendocrine tumor limited to the pancreas, which diffusely stained positive for insulin by immunohistochemistry (Fig 2). After surgery, she was euglycemic, and nonfasting insulin levels decreased to appropriate levels.

The Condition

Insulinoma is a rare neuroendocrine tumor, with an incidence of less than 5 per million people per year. (1) The mean age at diagnosis is 50 years, (2) making this pediatric presentation unique. This tumor causes hyperinsulinism and hypoglycemia, producing a clinical picture of repeated episodes of tremulousness, diaphoresis, confusion, and difficulty with arousability. In less than 10% of cases, the tumor is malignant or associated with MEN1. (2) Moreover, cases of pediatric insulinoma show an association with neurofibromatosis type 1 and tuberous sclerosis, (3) but our patient did not have the skin findings or other clinical manifestations of both diseases.

Congenital hyperinsulinism, a condition affecting β islet cells, also presents with hyperinsulinism and hypoglycemia

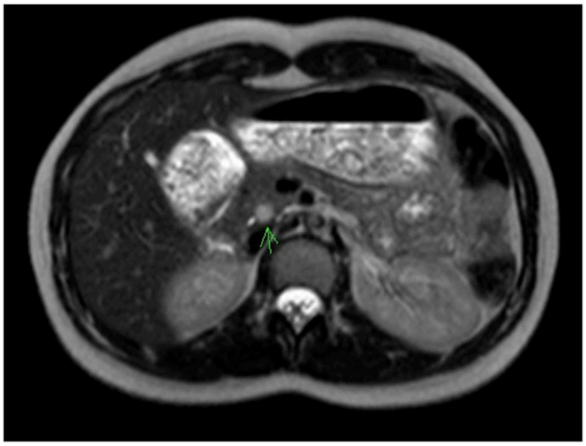

Figure 1. T2-Weighted axial magnetic resonance image of the abdomen showing a lesion (green arrow) at the head of the pancreas.

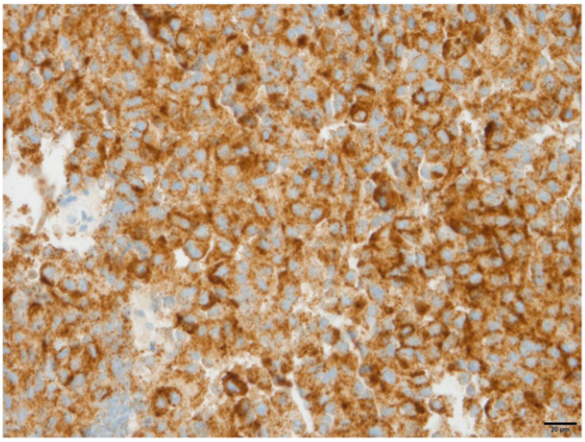

Figure 2. Lesion diffusely positive for insulin (insulin immunohistochemical stain, ×40).

in pediatric patients. However, this condition is primarily seen in patients younger than 18 months. Of the 2 subtypes, the diffuse is twice as common as the focal and represents a more complicated treatment challenge. (2)

Diagnosis

Historical diagnostic criteria for insulinoma, named the Whipple triad, include fasting hypoglycemia, symptoms of hypoglycemia, and resolution of symptoms with glucose administration. (4) Serum study–based diagnostic criteria may require a 72-hour fast with measurement of inappropriately elevated insulin or proinsulin levels and suppression of ketone levels. (5) Iatrogenic or factitious hypoglycemia can be evaluated with C-peptide and sulfonylurea levels.

Localization of the tumor is required to confirm the number and location of the tumor(s) and to guide surgical interventions. Insulinomas are typically singular and benign but may be multiple and scattered throughout the pancreas in cases associated with MEN1. Both CT and MRI are highly sensitive for insulinomas, especially larger ones. Arterial calcium stimulation of insulin release with venous sampling can aid in localization of smaller insulinomas to the appropriate region of the pancreas. (6) Although not widely available, the most useful imaging technique is 18F-DOPA positron emission tomography combined with enhanced CT. (7) Recent studies have also found this technique using gallium DOTA-(Tyr3)-octreotate (Ga-DOTATATE) to be a useful adjunct study when the results of other imaging studies are negative. (8) Endoscopic ultrasonography offers the possibility for fine-needle aspiration and histologic study of the tumor before resection, as was performed in our patient. Immunohistochemical studies for the presence of chromogranin A, insulin, synaptophysin, and Ki-67 are indicated. (9) Chromogranin A and synaptophysin are specific markers of neuroendocrine cells, and Ki-67 expression and mitotic index are used for grading. Some insulinoma samples may not stain positively for insulin, perhaps due to its rapid release from cells. (8)

Management

Surgical removal provides definitive treatment for insulinoma. The procedure involves enucleation and possibly removal of a portion of the pancreas. Rarely, complete pancreatectomy, and even a Whipple procedure, is performed for insulinoma. (2) It is typically an open procedure rather than laparoscopic. Intraoperative ultrasonography is routinely used to confirm tumor location. Ethanol ablation has been used successfully in some patients deemed prohibitively high risk for surgery. (10)

Medical management for patients who await, refuse, or are poor candidates for surgery is aimed at preventing symptomatic hypoglycemia. Diazoxide decreases insulin secretion but may cause edema and hirsutism. (2) At higher doses, somatostatin analogues such as octreotide inhibit the release of insulin but also of glucagon and growth hormone. (4)

Lessons for the Clinician

- Effects of (recurrent) hypoglycemia, when severe, can result in seizures, loss of consciousness, coma, brain damage, and even death, so early recognition and prompt treatment is imperative and warrants further investigation to determine the underlying cause.
- Insulinoma, seen mostly in adults, can also affect the pediatric population. Once a diagnosis has been established, definitive surgical treatment should be prioritized. Medical management is available for those who are poor surgical candidates or who are not interested in surgical treatment.
- Insulinoma is usually benign and not commonly related to multiple endocrine neoplasia type 1, neurofibromatosis type 1, or tuberous sclerosis syndromes.
- Accurate localization using different noninvasive imaging modalities, or in some cases use of intraoperative ultrasonography, is key to surgery planning and excision of tumor(s).

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4

Atypical Cause of Cyanosis While Bathing in an 18-month-old Boy

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AUTHOR DISCLOSURE Drs Maurice and Ellsworth have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-month-old boy with a medical history of cyanotic episodes presents with possible seizure activity at child care. When he was 10 months old, 8 months before presentation, he began having periods when he would become limp and cyanotic for a minute. The episodes would occur when bathing. There was no eye deviation noted, or shaking of extremities. Initially the episodes occurred once per month but have become more frequent, now with each occurrence of bathing. He has presented to an outside hospital, and was evaluated with brain magnetic resonance imaging and electroencephalography (EEG), which, per report, were reassuring, and he was discharged with no medications to follow up with a pediatrician. On the day of admission he had an episode of seizurelike activity, described as tonic-clonic activity of his upper and lower extremities, followed by a period of being nonresponsive and foaming at the mouth. This occurred after washing his hands at child care.

In the emergency department he is well appearing with normal vital signs. Evaluation includes a normal complete metabolic panel (including electrolyte levels and renal and liver function) with negative urine drug screen and head computed tomographic scan results. An inpatient test reveals the diagnosis.

DISCUSSION

While an inpatient, the patient undergoes video EEG with the addition of water exposure. During video EEG, the patient is given a sponge bath with his feet in water. The EEG recordings show intermittent theta frequency slowing, most prominently over the left centrotemporal region. When the mother places the patient's feet in water and begins to bathe him with a wet towel, the EEG shows simultaneous changes described as higher-amplitude delta frequency slowing over the left temporal region. This activity then spreads to involve the left frontocentral and temporal regions, followed by evolution with higher-amplitude and faster-frequency sharp waves or spike/wave activity, most prominent over the left frontotemporal region, consistent with epileptic activity. Clinically he initially has decreased responsiveness followed by decreased tone.

The Condition

This case highlights an uncommon cause known as reflex epilepsy triggered by the stimulus of hot water, or bathwater. Reflex seizures are seizures that are triggered by internal or external stimuli. This type of seizure composes 4% to 7% of those with epilepsy. (1) The trigger for reflex seizures can include visual (such as the flashing lights from video games), auditory, proprioceptive, and somatosensory stimuli, or even hot water. In general, the simple triggers, such as flashing lights, will trigger a seizure within seconds, whereas the more complex cognitive tasks, such as reading, will take minutes to trigger a seizure. (2) Bathing epilepsy is a rare type of reflex epilepsy in which the seizures are provoked from both tactile and heat stimuli. (3) It was first described in 1945, and since that time case series of patients have been reported around the world, with large numbers of patients from southern India, Japan, and Turkey. (4) Males are more commonly affected (2.6–3:1), and the range of age at onset is from 7 months to 13 years. (5) In a collection of 18 cases, the onset of seizure activity ranged from the time the patient touched the water to 60 seconds after initiation of bathing. (6)

Diagnosis

The diagnosis of bathing epilepsy first requires a history that would direct toward the diagnosis. Many patients have pallor, cyanosis, and hypotonia near the onset of bathing. To definitively diagnose this reflex epilepsy over other bath-induced paroxysmal disorders would require a video EEG during a bath.

Management

The first line of management is to decrease the temperature of the water, as that alone can resolve the seizures for some. For those who do not respond to lower-temperature water or changing the method of bathing, antiepileptic medications (frequently carbamazepine) can be initiated. (7)

Lessons for the Clinician

- Bathwater epilepsy can be a source of bathing-induced hypotonia and cyanosis.
- The diagnosis is confirmed using video electroencephalography while triggering a seizure.
- The first line of treatment is to decrease the temperature of the water; the second line is to administer antiepileptic medications.

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in Brief

Developmental Dysplasia of the Hip

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AUTHOR DISCLOSURE Drs Auriemma and Potisek have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Pediatricians may discover a click or a clunk when performing a physical examination of the neonatal hip. Assessment for developmental dysplasia of the hip (DDH) is a routine part of the neonatal examination because failure to detect neonatal hip instability or to respond appropriately to an abnormal examination may result in long-term disability for the child.

Developmental dysplasia of the hip covers a wide range of diseases related to abnormal development of the acetabulum and femoral head. The primary cause of DDH is improper fetal or postnatal positioning, which limits contact between the femoral head and the acetabulum, hindering proper growth. The resulting spectrum of disease extends from subtle abnormalities detected only on imaging through more severe manifestations such as dislocated hips that are unstable at rest.

With the lack of a standardized definition and the uncertain clinical relevance of particular imaging findings, the true incidence of DDH remains unclear. The incidence of DDH with dislocation is approximated to be 1 in every 1,000 live births; however, this likely represents an underestimate considering the full range of congenital hip disease. If mild dysplasia without dislocation is included, the overall incidence is approximately 1% of newborns; and when including any abnormality detected by screening ultrasonography, the incidence increases to 5% to 7%.

Factors that increase the risk of DDH include female sex, breech presentation, DDH in a first-degree relative, and improper swaddling methods. It occurs in females up to 4 times more often than in males. Breech presentation is reported in 17% to 23% of cases. Frank breech presentation confers the highest risk and occurs when the fetal hips are in flexion and both knees are extended with the feet in close proximity to the head. Breech presentation occurs in approximately 1 in 25 term births, with more than half being frank breech. At what point before delivery spontaneous or external cephalic version decreases the risk of DDH remains unclear. Although breech presentation is so strong a risk factor, breech-born infants with DDH may have better outcomes than non–breech-born infants. Recent evidence suggests that DDH related to breech positioning may have a higher propensity toward spontaneous resolution. Removing the infant from the in utero breech position may alleviate strain on the joint capsule, allowing the hip to stabilize naturally. Interestingly, breech presentation in twins does not seem to increase the risk of DDH compared with singleton pregnancies. Breech twins often have their knees flexed, whereas breech singleton fetuses are more likely to be in frank breech position, with knees extended. Family history is another factor in stratifying the risk of DDH, as infants with an affected parent or sibling are at 12 times higher risk. In twin gestations, genetics also plays a strong role: if a monozygotic twin has DDH, the risk of the other twin being affected is approximately 40%. Last, improper swaddling may force an infant's hips into

Evaluation and Referral for Developmental Dysplasia of the Hip in Infants. Shaw BA, Segal LS. *Pediatrics.* 2016;138(6)

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extension and adduction, increasing the risk of DDH. A hip healthy swaddling technique should be followed, allowing sufficient space for the hips to move and the knees to be slightly flexed. Although risk factors are additive, in 3 of 4 affected infants the only risk factor is female sex.

Careful examination of the hips is an essential aspect of screening and surveillance of DDH. The appropriate test depends on the infant's age. In the first 3 months of life, the Ortolani and Barlow maneuvers are the standard examinations, and they should be performed on a relaxed infant laying supine on a flat surface with the hips flexed to 90°. The examiner's thumb should rest on the inner thigh while the index and middle fingers apply pressure over the greater trochanter area. To perform the Ortolani maneuver, the hip is abducted with simultaneous anterior pressure on the trochanter. A positive test occurs when a "clunk" is felt as the head of the dislocated femoral head travels over the posterior acetabular cartilage and reduces back into the hip socket. The Barlow maneuver is performed by adducting the hip while palpating for the head of the femur dislocating from the socket. Dislocating a hip with the Barlow maneuver does not necessarily indicate future dislocation or predict DDH. With maturation of the acetabulum and reduced laxity of the joint capsule, a positive Barlow typically resolves spontaneously after 2 weeks. An audible "click," rather than a felt "clunk," during either maneuver is considered normal and represents snapping of soft tissue.

After 3 months of age the Barlow and Ortolani tests are poorly sensitive because affected hips have likely become fixed in the dislocated position. If hip dysplasia is unilateral, the Galeazzi sign may be present. In this test, the infant lays supine on the examining surface with knees flexed to 90° and feet planted flat on the surface. Ankles should be brought back into contact with the buttocks. Asymmetry in the level of the knees is considered a positive test. Asymmetrical thigh and gluteal folds may be supportive evidence of DDH in the context of other abnormal findings, but as isolated findings they are poorly predictive. With bilateral hip dysplasia, no asymmetry in the level of the knees may be evident, and restricted range of motion of the hips may be the only positive finding on examination.

For the first 3 months of life, ultrasonography is the imaging modality of choice for evaluation of DDH because ossification of the femoral head does not usually occur until 4 months of age. Then, an anteroposterior plain radiograph can identify asymmetry, subluxation, or frank dislocation. When best to obtain an imaging study is not well-defined, but the decision should be guided by the physical examination findings. In infants with abnormal examination findings concerning for possible DDH, ultrasonography should be considered by 3 to 4 weeks of age. For an infant with risk factors for DDH but normal hip examination findings, waiting until 6 weeks of age may reduce false-positive ultrasonography results. Imaging should be obtained by 6 months of age. A dislocated hip (positive Ortolani test result) requires referral but does not necessarily need imaging before treatment. Imaging may be obtained at the discretion of the provider with shared decision making with the parents, taking into consideration radiation exposure and cost.

The cornerstone of treatment for DDH is abduction bracing, typically reserved for infants with an unstable hip on examination. An infant with an abnormality on imaging but normal examination findings warrants close follow-up, with treatment deferred because most minor findings on ultrasonography resolve spontaneously by 6 months of age. Although the evidence to support one bracing technique over another is limited, the Pavlik harness is most commonly used. With soft straps and Velcro, the harness keeps the hips flexed and abducted, reducing the dislocation and promoting healthy development of the acetabulum. Bracing should ideally be started in the first 9 weeks of life and no later than 5 months of age to increase the likelihood of success. Well-described risks from Pavlik harnesses include femoral head avascular necrosis and femoral nerve palsy. If treatment with a Pavlik harness is unsuccessful in reducing the hip after 3 weeks, closed reduction with subsequent spica cast application is typically attempted. Once a child is 18 months old, an open surgical repair is usually needed to achieve full reduction of a dislocated hip.

When untreated, DDH can leave a child with a leg length discrepancy, a limp or waddling gait, and reduced range of motion of the hip joint. In older children and adolescents, symptoms may be alleviated with a periacetabular osteotomy. However, untreated DDH remains a major contributor to secondary osteoarthritis in adults and potentially can lead to total hip arthroplasty with variable outcomes.

COMMENT: Not too long after magnetic resonance imaging (MRI) became a standard mode in the evaluation of low back pain, a clever study looked at the results of MRI in a group of young adults with low back pain and a control group of age-matched people with no such history. Lo and behold, the prevalence of bulging discs was the same in both groups. What then does the finding on imaging really mean clinically? I suspect that far too many MRIs are still acquired to investigate back pain, and I have to wonder how many interventions are then initiated based on an imaging finding that may in fact be irrelevant. And so it may be with ultrasonography and infants' hips. In 2016 the American Academy of Pediatrics issued the clinical report on the evaluation of DDH cited by Drs Auriemma and Potisek, acknowledging that "…there is a lack of agreement on ultrasonic diagnostic criteria for DDH as a disease versus developmental variations." Ultrasonography certainly has an important role in evaluating possible DDH, but how often, we need to ask, do findings on ultrasonography that would resolve with time lead instead to intervention? And how many of such ultrasonographic evaluations were ordered in the first place on the basis of a "click" rather than a "clunk"?

– Henry M. Adam, MD
Associate Editor, *In Brief*

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***Campylobacter* Infections in Children:** 1. C; 2. B; 3. B; 4. D; 5. D.

Pediatric Gastritis, Gastropathy, and Peptic Ulcer Disease: 1. E; 2. B; 3. B; 4. D; 5. D.

Effect of Maternal Substance Abuse on the Fetus, Neonate, and Child: 1. A; 2. D; 3. D; 4. C; 5. E.

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Visual Diagnosis

Circumscribed Pigmentation Stippled with Punctate Macules and Papules in a 9-year-old Boy

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†Toronto Dermatology Centre, Toronto, Ontario, Canada

PRESENTATION

A 9-year-old Chinese boy presents with an asymptomatic giant hyperpigmented patch on his back that has been present since birth. The parents were told that this is a café-au-lait patch and that by itself it is of no medical significance. They were advised to keep an eye on the future appearance of similar lesions, 6 or more of which measuring 0.5 cm or larger may signify neurofibromatosis, a neurocutaneous disorder. Speckled, dark, superimposed spots were seen in this patch at 2 years of age. Over the subsequent years, the dark spots have gradually increased in size and number. Some of dark spots have become elevated.

The child was born to a 28-year-old gravida 3 para 2 mother at 39 weeks' gestation after an uncomplicated pregnancy and a normal vaginal delivery. The parents are healthy and nonconsanguineous. There is no family history of similar lesions, dysplastic nevus, melanoma, or neurofibromatosis. His developmental milestones and past health are normal.

On examination there is a sharply demarcated, well-circumscribed, light tan elliptical patch on the lower back (Fig 1). Numerous speckled, dark macules and papules as well as 2 plaques are seen in the patch. The remaining examination findings are normal. There is no other cutaneous or systemic abnormality.

AUTHOR DISCLOSURE Dr Leung has disclosed no financial relationships relevant to this article. Dr Barankin has disclosed that he receives honoraria for giving CME talks from AbbVie, Galderma, Leo Pharma, Janssen, Valeant, Pierre Fabre, La Roche-Posay, Novartis, Celgene, Eli Lilly, Amgen, Actelion, Cipher Pharma, Beiersdorf Canada, and Tribute Pharma. The commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DIAGNOSIS

The patient has a nevus spilus, also known as speckled lentiginous nevus. The diagnosis is mainly clinical, based on the physical findings of dark punctate macules and papules over a background of well-circumscribed tan pigmentation.

Discussion

Nevus spilus occurs in less than 0.2% of newborn infants. The reported prevalence in the pediatric age group ranges from 1.3% to 2.1%, and that in the adult population is approximately 2.3%. The sex incidence is approximately equal. All ethnic and racial groups are at risk, but there is a slight predilection for white individuals. Presumably, nevus spilus results from a localized defect in

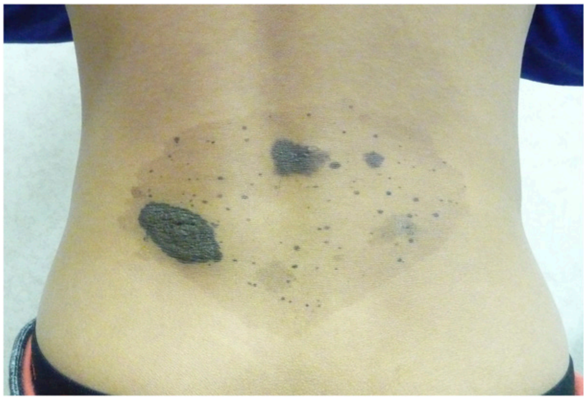

Figure 1. A giant nevus spilus on the lower back of a 9-year-old boy.

neural crest melanoblasts under the influence of environmental and genetic factors.

Typically, nevus spilus presents as an asymptomatic, tan to brown, sharply demarcated, well-circumscribed pigmentation that is studded with multiple, smaller, darker punctate macules or papules. The condition can be congenital or, more commonly, acquired. Acquired lesions usually develop in the first year of life. The lesion often starts as a light-brown oval macule/patch with few or no speckles. Over time, the speckles slowly increase in size and number. These speckles can be macular or papular and represent lentigines or melanocytic nevi. The number of speckles usually ranges from 8 to 10, and the size of speckles ranges from 1 to 3 mm. Nevus spilus, similar to melanocytic nevus, is classified as small (<1.5 cm), medium or intermediate (1.5–19.9 cm), and large or giant (≥20 cm) according to their expected greatest diameter in adulthood. In the present case, the nevus spilus is considered to be giant. In most cases, the lesion is small or medium and solitary (Figs 2 and 3). Sites of predilection include the trunk and extremities. Nevus spilus can be segmental or zosteriform. The condition is usually nonhairy, although hairy nevus spilus has rarely been reported. Typically, nevus spilus is an isolated finding. Nevus spilus has been reported in association with blue nevus, Spitz nevus, nevus depigmentosus, nevus sebaceous, nevus of Ito, and centrofacial lentiginosis. Rarely, nevus spilus may occur as part of phacomatosis pigmentokeratotica, phacomatosis pigmentovascularis, phacomatosis spilorosea, nevus spilus syndrome, or FACES (*f*acial features, *a*norexia, *c*achexia, *e*ye anomalies, *s*kin anomalies) syndrome.

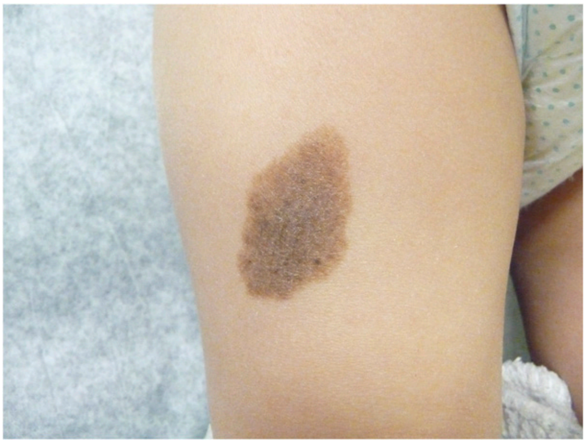

Figure 2. Nevus spilus on the right thigh of a 5-year-old girl.

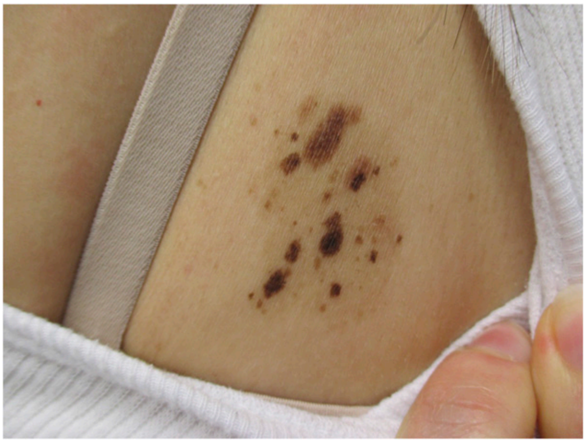

Figure 3. Nevus spilus on the right upper back of a 28-year-old woman.

The diagnosis is mainly clinical based on the characteristic findings. Dermoscopy and in vivo confocal microscopy may aid in the diagnosis.

The differential diagnosis includes café-au-lait spot, agminated (grouped together) lentiginosis, agminated nevomelanocytic nevi, Becker nevus, and linear and whorled nevoid hypermelanosis. A café-au-lait spot/patch presents as an ovoid, uniformly brown macule/patch in the absence of intralesional speckled macules or papules (Fig 4). In

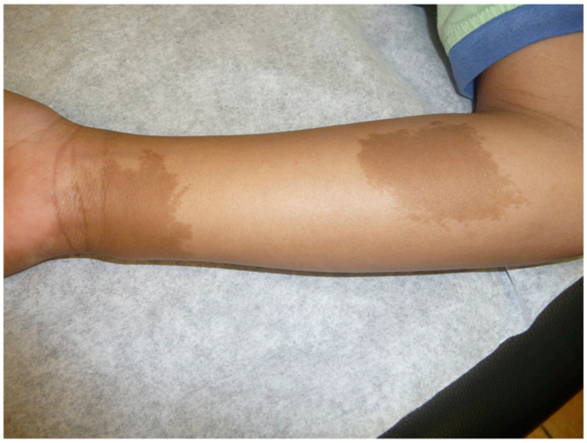

Figure 4. Café-au-lait patches presenting as uniform brown patches in the absence of intralesional speckled macules or papules on the right forearm of a 10-year-old boy.

agminated lentiginosis and agminated nevomelanocytic nevi, macules or papules occur on normal-appearing skin without background pigmentation. A Becker nevus consists of a sharply demarcated, irregular area of hyperpigmentation without any speckled pattern; hypertrichosis in the lesion occurs in approximately 17% of patients (Fig 5). In addition, onset of the Becker nevus is usually around puberty and not early childhood. Linear and whorled nevoid hypermelanosis is characterized by linear streaks and swirls of macular hyperpigmentation in a reticulate pattern along the lines of Blaschko without any preceding inflammatory or palpable verruciform lesions. Superimposed macules and papules are characteristically absent.

Nevus spilus can be cosmetically unsightly and embarrassing and may cause undue parental anxiety. This is especially so if the lesion is large and occurs on an exposed area. Patients with nevus spilus are at low risk for melanoma; atypical melanocytic proliferations can lead to melanoma formation.

Although nevus spilus is generally benign, affected patients require regular lifelong follow-up so that any changes that are suspicious for malignancy can be detected and treated early. This is especially so for patients with giant or zosteriform nevus spilus and nevus spilus with an atypical appearance. Dermoscopy, in vivo confocal microscopy if available, and serial photography at least annually can be helpful for monitoring. If doubt exists, a biopsy of the lesion for histologic examination should be considered. Routine prophylactic excision of the lesion is not justified and not supported by the existing literature. On the other hand, prophylactic full-thickness complete excision of the lesion should be considered in the setting of dysplasia or if an atypical appearance is noted. Treatment should also be considered if there is undue cosmetic concern. Fractional CO_2 laser combined with Q-switched Nd:YAG laser is a therapeutic option.

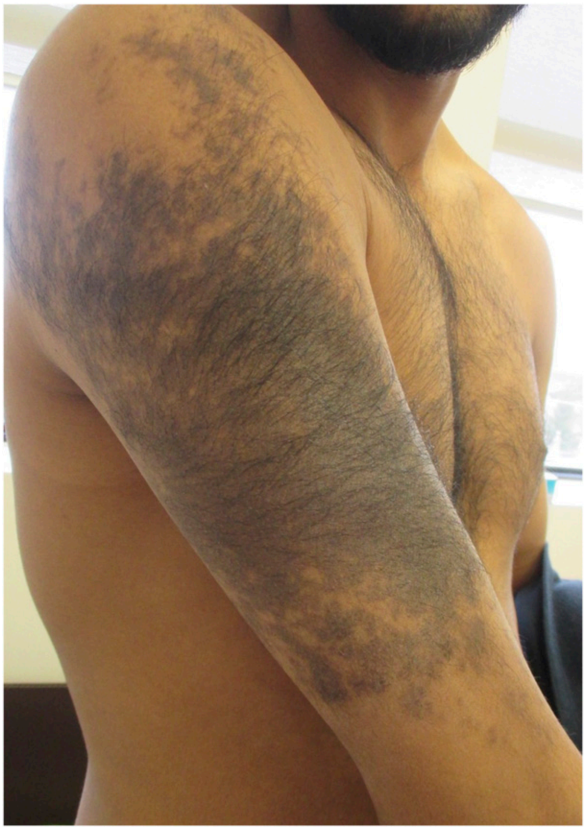

Figure 5. A Becker nevus presenting a sharply demarcated, irregular area of hyperpigmentation without any speckled pattern. Note hypertrichosis in the lesion.

Patient Course

Dermoscopy was negative for dysplastic nevus or melanoma. Histopathologic examination of a biopsy specimen of the patch showed an increase in melanin deposition in keratinocytes and an increase in the number of nonnested melanocytes along the basal cell layer of the epidermis. The papular and plaque component showed melanocytic nests in the dermoepidermal junction as well as in the dermis (compound nevus) with no atypia. The parents were reassured that the lesion was generally benign, and dermoscopic follow-up was arranged annually to monitor for any changes that may be suspicious for potential malignancy. Serial photography and repeated measurement of the lesion were also performed at the follow-up visits. At his 3-year follow-up visit, the child appeared healthy, and dermoscopy did not show signs of malignancy.

Summary

- Nevus spilus presents as an asymptomatic, tan to brown, sharply demarcated, well-circumscribed pigmentation that is studded with multiple, smaller, darker punctate macules or papules.
- Patients with nevus spilus are at low risk for melanoma.
- Affected patients require regular lifelong follow-up so that any changes that are suspicious for malignancy can be detected and treated early.
- Dermoscopy, in vivo confocal microscopy if available, and serial photography at least annually (particularly for large lesions) can be helpful for monitoring. If doubt exists, biopsy of the lesion for histologic examination should be considered.
- Routine prophylactic excision of the lesion is not justified.

Suggested Readings

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Visual Diagnosis

Severe Ulceronecrotic Eruption with Systemic Symptoms

Kevin Kilgallon, MD,[*] Jagadisharaje Urs, MD,[*] Esteban Fernandez Faith, MD[†]

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AUTHOR DISCLOSURE Dr Kilgallon has disclosed that he has a family member who is employed by AbbVie. Dr Urs has disclosed no financial relationships relevant to this article. Dr Fernandez Faith has disclosed that he has research grants from the Pediatric Research Alliance and The Society for Pediatric Dermatology to study ulcerated hemangiomas. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy with a worsening skin eruption presents to a primary care clinic for a follow-up visit after a recent evaluation in the emergency department. The rash started 3 weeks earlier and continues to worsen despite supportive care and a short course of oral corticosteroids. The rash started on his left abdomen and quickly spread, becoming generalized. There are also multiple erythematous papules and plaques with large hemorrhagic crusts leaving punched out ulcerations on the neck, axillae, trunk, upper and lower extremities, buttocks, inguinal folds, and genitals (Fig). Similar but fewer lesions are present on the face. There are multiple purpuric papules with central vesicles involving the legs and dorsal feet. Palms, soles, and mucous membranes are not involved. In the past week, he reports having subjective fevers, abdominal pain, and diarrhea. His growth chart also shows an 8.1-lb (3.7-kg) weight loss in the past 17 days. Due to the appearance and severity of the rash, he is emergently referred to and evaluated in the dermatology clinic later that day. Punch biopsy samples are obtained of the recent and more established lesions.

Due to the ill appearance of the patient, the presence of systemic symptoms, the severity of the eruption, and the dehydration on examination, the patient is admitted to the hospital for diagnostic evaluation and treatment. The clinical presentation and skin biopsy results confirm the diagnosis.

DIAGNOSIS

The acute presentation and rapid progression of severe ulceronecrotic lesions with a generalized distribution and systemic symptoms raise the suspicion of a severe form of pityriasis lichenoides et varioliformis acuta (PLEVA) known as febrile ulceronecrotic Mucha-Habermann disease (FUMHD).

His evaluation shows a normal white blood cell count with mild anemia and an elevated erythrocyte sedimentation rate at 23 mm/hour with a normal C-reactive protein level. Results of testing for herpes simplex virus, varicella-zoster virus, and enterovirus by polymerase chain reaction from cutaneous lesions and blood are negative. Results of a respiratory viral panel, adenovirus, mycoplasma polymerase chain reaction from throat swab, and human immunodeficiency virus testing are also negative. An immunologic evaluation, including antinuclear antibody testing, antineutrophil cytoplasmic antibodies, myeloperoxidase antibodies, proteinase-3 antibodies, and fecal calprotectin, shows no abnormalities other than weakly positive antinuclear antibody at 1:160.

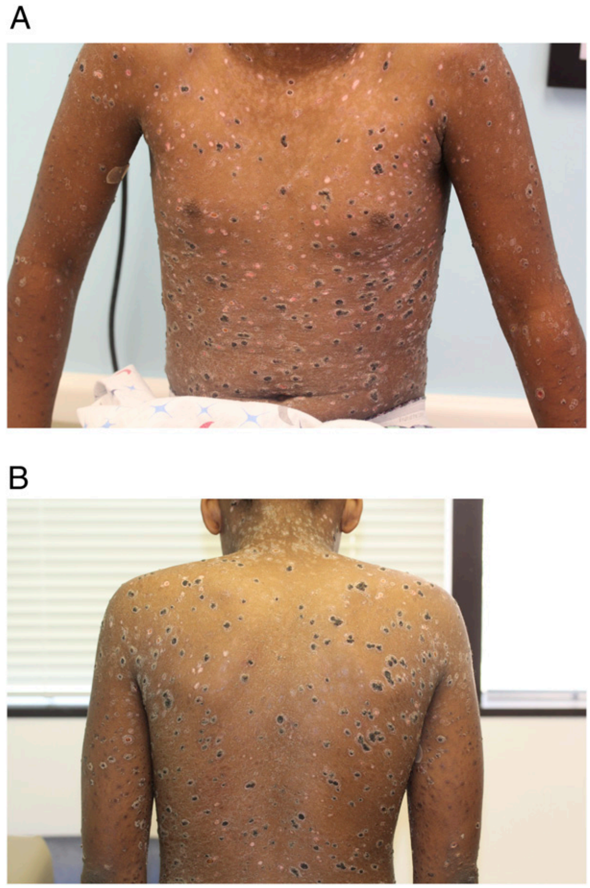

Figure. Ulceronecrotic skin findings on the chest and arms (A) and back (B) at initial presentation.

Dermatopathologic analysis of the skin biopsy sample shows necrotic epidermis with prominent hemorrhagic crust and associated hyperkeratosis and parakeratosis. There is a superficial and deep perivascular lymphocytic infiltrate with extravasation of erythrocytes and exocytosis. These findings, along with the clinical presentation, are consistent with FUMHD.

Discussion

As an acute inflammatory skin disorder, PLEVA is characterized by the development of small (2- to 3-mm) erythematous macules and papules that quickly evolve into papulovesicular and necrotic papules with central crusting. These lesions exist at different stages of development simultaneously and gradually resolve, often leaving a varioliform scar and postinflammatory dyspigmentation. Symmetrical involvement on the trunk, extremities, and flexural areas is typical, but the pattern can be generalized as well. (1) Occasionally, fever and systemic symptoms may be associated.

As a rare variant of PLEVA, FUMHD is characterized by rapid progression of large ulceronecrotic nodules and plaques associated with high fever. (2) It is a severe and potentially lethal variant of PLEVA. To date, 71 cases of FUMHD have been reported, 37 of which were in children, (3)(4) and FUMHD exhibits a male predominance (approximately 2:1 male-to-female ratio). It can start with skin changes associated with PLEVA that evolve into large coalescent ulceronecrotic lesions, or it can have a more acute onset of large papulonecrotic lesions covering nearly the entire body. Oral, genital, and conjunctival tissue can be affected. The disease is characterized by high fever and can be associated with other systemic symptoms, including gastrointestinal, neurologic, pulmonary, hematologic, and rheumatologic manifestations. Skin lesions often become superinfected, adding to the complexity and severity of this condition. Mortality can be as high as 20%, with nearly all of the mortality seen in adults older than 40 years. (5) One recent case reported death from FUMHD in a 9-year-old boy after superinfection of his skin lesions with *Pseudomonas aeruginosa* and subsequent sepsis. (3)

Although the etiology of FUMHD is unknown, different theories have been proposed. Theories include a hypersensitivity reaction (to an infectious agent such as cytomegalovirus, Epstein-Barr virus, or adenovirus), an autoimmune process, or a variant of cutaneous T-cell lymphoma. (5)(6)

The clinical differential diagnosis includes small vessel vasculitis (Henoch-Schönlein purpura), erythema multiforme, Stevens-Johnson syndrome, and a primary viral infectious etiology such as varicella and atypical Coxsackie infection.

Management

There is no agreed-on standard treatment for FUMHD. Treatment modalities include phototherapy, systemic antibiotics, systemic corticosteroids, methotrexate, dapsone, pentoxifylline, intravenous immunoglobulins, cyclosporine, and anti–tumor necrosis factor α (TNF-α) agents. Several cases have been successfully treated with a course of low-dose methotrexate along with systemic corticosteroids. (5) Treatment with TNF-α inhibitors may represent a first-line option in the future, as elevated TNF-α levels have been reported in patients with FUMHD. (2)

Patient Course

On admission the patient is treated with intravenous (IV) fluids, triamcinolone 0.1% ointment, azithromycin, wound care, and pain control. Once infectious etiologies are ruled out, he is started on IV methylprednisolone at 1 mg/kg per day for 3 days and weekly methotrexate 12.5 mg orally. Within 2 days of hospitalization new cutaneous lesions cease to appear and his systemic symptoms significantly improve. After 3 days of receiving IV corticosteroids he is transitioned to oral prednisone to gradually taper down the dose over 4 weeks. He is afebrile throughout hospitalization.

His hospitalization is complicated with methicillin-susceptible *S aureus* bacteremia likely secondary to cutaneous superinfection. This is treated with IV cefazolin and later transitioned to cephalexin to complete a 10-day course.

At an outpatient dermatology follow-up appointment 2 weeks after discharge, continued improvement is noted. Appetite and weight are improving (he had gained 9.7 lb [4.4 kg] since admission), and the eruption is significantly improved. There is hypopigmentation and scattered depressed scars at sites of previous involvement. His prednisone is tapered and discontinued. He continues on a weekly dose of 12.5 mg of methotrexate along with folic acid supplementation.

Summary

- Pityriasis lichenoides et varioliformis acuta (PLEVA) is a rare inflammatory skin disorder characterized by the development of erythematous macules and papules on the trunk, extremities, and flexural areas that evolve into papulovesicular lesions that become ulcerated and crusted.
- Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a very rare and acute form of PLEVA characterized by ulceronecrotic nodules and plaques along with fever, systemic symptoms, and a rapid course that can be debilitating and deadly.
- It is important to rule out infectious causes, vasculitis, erythema multiforme, and Stevens-Johnson syndrome when considering a diagnosis of PLEVA and FUMHD.
- There is no standard treatment, but therapy includes supportive care along with systemic immunosuppressants.

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Suggested Readings

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Hematuria and Proteinuria in Children

Bernarda Viteri, MD,* Jessica Reid-Adam, MD*

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Practice Gap

Pediatricians must be aware of screening indications and the evaluation and management of a child with hematuria and/or proteinuria.

Objectives

After completing this article, readers should be able to:

1. Understand the common causes of proteinuria and hematuria and be able to differentiate between benign and serious causes.
2. Describe screening techniques for initial evaluation of hematuria and proteinuria.
3. Recognize the criteria for diagnosis of proteinuria and hematuria.
4. Plan the appropriate initial evaluation for hematuria and proteinuria and interpret laboratory findings essential for diagnosis.
5. Recognize serious causes of hematuria and proteinuria that warrant immediate referral.

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ABBREVIATIONS

AS	Alport syndrome
CKD	chronic kidney disease
CNS	congenital nephrotic syndrome
ESRD	end-stage renal disease
FSGS	focal segmental glomerular sclerosis
GN	glomerulonephritis
HSP	Henoch-Schönlein purpura
HPF	high-power field
Ig	immunoglobulin
LMW	low molecular weight
MCD	minimal change disease
RBC	red blood cell
SLE	systemic lupus erythematosus
UA	urinalysis
U p/c	urine protein/creatinine ratio

INTRODUCTION

Hematuria and proteinuria are common findings in primary care practice. Although the American Academy of Pediatrics eliminated routine urine screening from its preventive care guidelines a decade ago, many pediatricians continue to use screening urinalysis (UA) as part of their health supervision visits. Most pediatric patients who are diagnosed as having hematuria or proteinuria through screening UA do not have renal disease, and abnormal findings usually resolve on repeated testing. However, hematuria or proteinuria that persists on repeated testing warrants additional evaluation, and, depending on history along with initial evaluation in the primary care office, may warrant referral to a pediatric nephrologist for further management. Although guidelines put forth by the American Academy of Pediatrics do not recommend yearly evaluation of urine by dipstick analysis for children, regular routine screening of pediatric populations has been established in Japan, Taiwan, and Korea. (1)(2)(3)(4) Our practice recommends screening of certain patient populations at increased risk for renal disease over a lifetime (Table 1).

The 2 most common tests used by clinicians for initial assessment of renal function or renal injury are the urine dipstick test and UA with microscopy, where urine is centrifuged, supernatant is removed, and urine sediment is examined

TABLE 1. Conditions Under Which Children Should Have a Yearly Urinalysis Performed

History of prematurity (<32 weeks' gestational age), very low birthweight, other neonatal complications requiring intensive care, umbilical artery line
Congenital heart disease (repaired or unrepaired)
Recurrent urinary tract infections, hematuria, or proteinuria
Known renal disease or urologic malformations
Solid organ transplant
Malignancy or bone marrow transplant
History of or prolonged treatment with drugs known to be nephrotoxic
History of recurrent episodes of acute kidney injury
Family history of inherited renal disease

Adapted from refs 5 and 6.

under a microscope. Whereas UA with microscopy is laboratory dependent, the dipstick test can be performed quickly in the provider's office and can guide the clinician to evaluate the patient further. Urine dipstick testing should be performed on a freshly voided urine sample, within 2 hours of collection; if a specimen needs to be refrigerated, it should be allowed to return to room temperature before testing. All pads of the dipstick are fully immersed in the urine and then immediately removed from the specimen cup and placed on a horizontal surface; results should be read within 1 minute, either manually or by automated analyzer. Providers should be aware that there are a variety of urine reagent strips on the market, with a range of semiquantitative concentration results that are not interchangeable between manufacturers.

The urine dipstick tests for the peroxidase activity of hemoglobin (or myoglobin); thus, a dipstick that is positive for blood is actually positive for the detection of heme pigment, which may reflect red blood cells (RBCs) in the urine or other causes, such as hemoglobinuria or myoglobinuria. A colorimetric test is used for detection of urine protein. The dipstick measures albumin concentration as a surrogate for protein, turning different shades of green, and, ultimately, blue, according to the concentration of albumin that reacts with tetrabromophenol. Whereas the urine dipstick is usually the initial screening test for both hematuria and proteinuria, additional studies are used to better quantify and characterize abnormal dipstick test findings. These additional studies are discussed further in this review.

HEMATURIA

Prevalence

Hematuria, a finding not uncommon to pediatricians, can be benign or can be a sign of a serious underlying condition. Population studies from the 1970s to the 1990s of school-aged children suggest that approximately 1% of them have 2 or more urine dipstick tests positive for microscopic hematuria, with persistence of hematuria at 6 months in one-third of this population. (2)(3)(4)

Definitions and Measurement Methods

Macroscopic hematuria is characterized by the presence of blood in the urine in sufficient quantity to be visible to the naked eye. Grossly bloody urine may appear pink or red but may also be tea-colored or dark cola-colored with glomerular etiologies. As little as 1 mL of blood per liter of urine can induce a visible color change, and as little as 2 to 3 RBCs per high-power field (HPF) can make the urine dipstick positive. (7)(8) To our knowledge, there are no published data that correlate the number of urine sediment RBCs with the dipstick result 0-3+.

On the other hand, microscopic hematuria is hematuria in the absence of visible color change in the urine, detected only by urine dipstick and confirmed by microscopic examination of the spun urine sediment. The definition of microscopic hematuria varies from 1 to 10 RBC/HPF; however, based on previous studies in school-aged children, we define microscopic hematuria as greater than 5 RBC/mm^3 in uncentrifuged urine or greater than 5 RBCs/HPF in centrifuged urine on at least 2 to 3 different occasions. Microscopic hematuria that might undergo further evaluation should be independent of trauma, exercise, menstruation, or sexual activity (Fig 1). (9)(10)(11)(12)(13)

When gross hematuria is suspected due to a change in urine color, the first step in evaluation is centrifuging a fresh sample of the discolored urine. A positive urine dipstick that results from myoglobinuria, as in the case of increased skeletal muscle breakdown (eg, rhabdomyolysis, extreme exercise, or myopathies) or hemoglobinuria (from rapid hemolysis), is typically associated with discolored urine (red supernatant after centrifugation) without RBCs noted on microscopic evaluation. On the other hand, discolored urine with a negative urine dipstick should prompt questioning for and/or inclusion of other pigments (food coloring, beets, blackberries, rhubarb, paprika); drugs (sulfonamides, nitrofurantoin, salicylates, pyridium, phenytoin, rifampin, chloroquine, defuroxamine, iron sorbitol); toxins (lead,

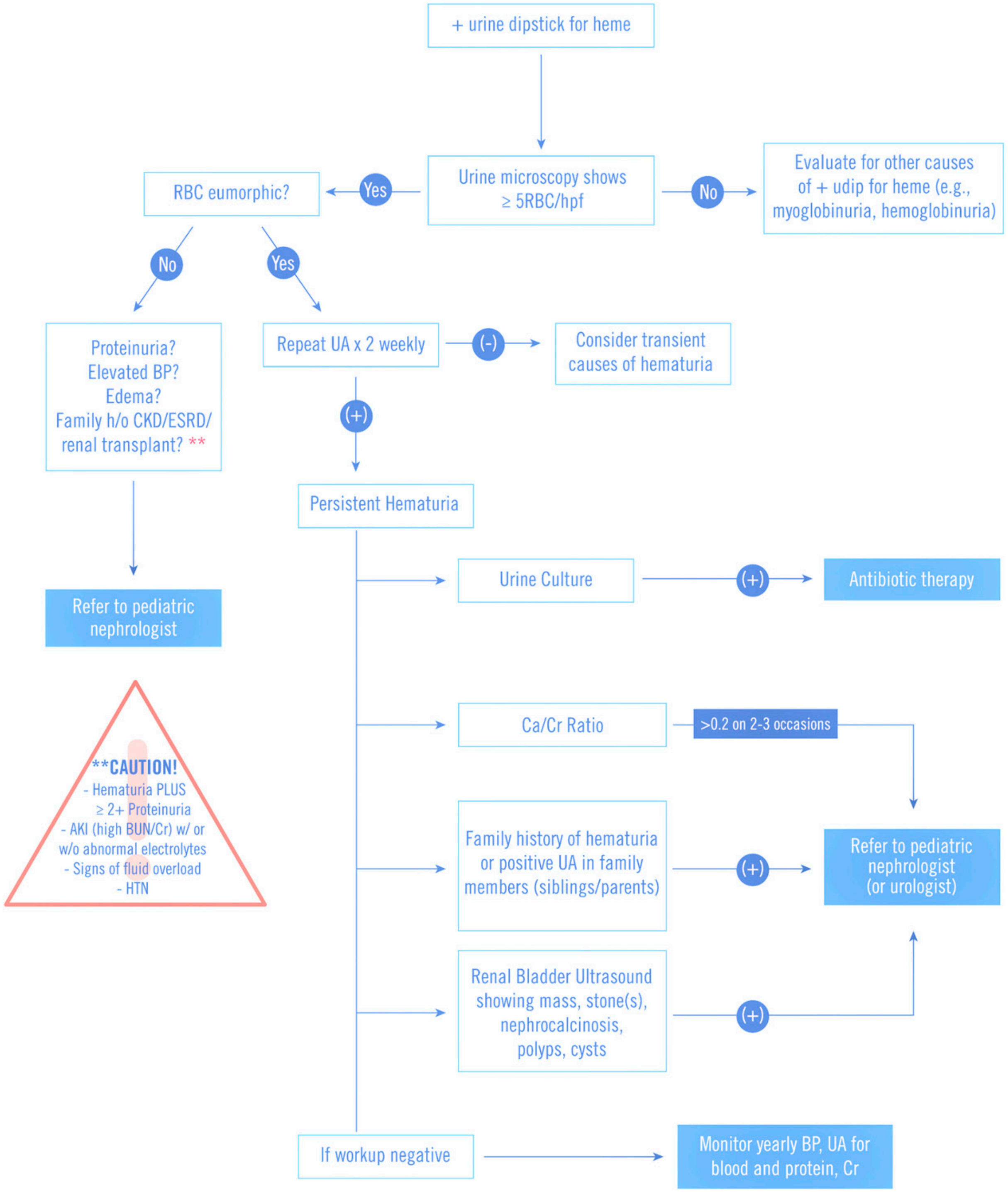
+ urine dipstick for heme
Urine microscopy shows ≥ 5RBC/hpf
Yes
RBC eumorphic?
No
Evaluate for other causes of + udip for heme (e.g., myoglobinuria, hemoglobinuria)
No
Yes
Proteinuria? Elevated BP? Edema? Family h/o CKD/ESRD/ renal transplant? **
Repeat UA x 2 weekly
(-)
Consider transient causes of hematuria
(+)
Persistent Hematuria
Refer to pediatric nephrologist
Urine Culture
(+)
Antibiotic therapy
**CAUTION!
- Hematuria PLUS ≥ 2+ Proteinuria
- AKI (high BUN/Cr) w/ or w/o abnormal electrolytes
- Signs of fluid overload
- HTN
Ca/Cr Ratio
>0.2 on 2-3 occasions
Family history of hematuria or positive UA in family members (siblings/parents)
(+)
Refer to pediatric nephrologist (or urologist)
Renal Bladder Ultrasound showing mass, stone(s), nephrocalcinosis, polyps, cysts
(+)
If workup negative
Monitor yearly BP, UA for blood and protein, Cr

Figure 1. Approach to a child with microscopic hematuria. Caution items warrant urgent consultation with a nephrologist. AKI=acute kidney injury; BP=blood pressure; BUN=blood urea nitrogen; CKD= chronic kidney disease; Cr=creatinine; ESRD=end-stage renal disease; HTN=hypertension; UA=urinalysis. (Adapted from refs 14, 15, 16, and 17)

benzene); and metabolites (homogenistic acid, tyrosinosis, urates) in the differential diagnosis. (14) One of the most common of these is the pink/orange discoloration of infant diapers as a result of urate crystal precipitation. (13)

Classification

Hematuria can be transient or persistent. In obtaining a comprehensive clinical history one should determine change in color of urine, timing of color change related to urinary stream, the pattern of the hematuria (transient or persistent), and associated signs, symptoms, illness, or activity. Transient hematuria has been found in association with fever, exercise, urinary tract infections (which usually also present with dysuria and pyuria), and trauma. Passage of fresh blood with or without clots at the beginning or end of the urinary stream should prompt consideration of lower urinary tract origin, with urethritis, trauma, bladder calculus or mass, and schistosomiasis as possible etiologies. (13) A detailed history of presentation should prompt a search for associated findings (Table 2).

Persistent hematuria is defined as more than 4 to 6 weeks of positive UA results showing more than 5 RBC/HPF in the absence of exercise activity, menses, or trauma and can be categorized based on whether the hematuria is glomerular or nonglomerular in origin (Table 2).

Nonglomerular Causes of Hematuria

Hypercalciuria, defined in children older than 2 years of age as a urine calcium/creatinine ratio greater than 0.2 (mg/mg), has been associated with persistent asymptomatic microscopic hematuria. Because infants are known to have higher calcium excretion combined with a lower urine creatinine level, a urine calcium/creatinine ratio less than 0.8 is deemed acceptable for infants younger than 6 months and less than 0.6 for infants 6 to 12 months old. Hypercalciuria may be an isolated finding or may be associated with nephrocalcinosis or frank stone disease. A recent retrospective cohort from the United Kingdom noted hypercalciuria in up to 15% of 511 children with nephrolithiasis, although other groups have described hypercalciuria in patients with urolithiasis to varying degrees, from 7% to 34%. (18)

Nephrolithiasis may be associated with microscopic or macroscopic hematuria, and depending on the location of the stone may also be associated with moderate to severe abdominal and flank pain. Nephrocalcinosis is usually asymptomatic and discovered as an incidental finding on imaging tests, or otherwise discovered on imaging during an evaluation for microscopic hematuria.

Nutcracker syndrome is a vascular disorder characterized by compression of the left renal vein between the aorta and proximal superior mesenteric artery. Although Nutcracker syndrome is not common in the United States, studies in Japanese and Korean children have found up to 30% to 45% of Doppler ultrasonographic findings consistent with Nutcracker syndrome in the setting of unexplained hematuria. (19)(20) Although most often asymptomatic, this phenomenon can present with left flank pain or abdominal pain, hematuria (which is more often microscopic than macroscopic), and varicocele. The venous compression in Nutcracker syndrome may be detected by Doppler ultrasonography or by computed tomography/magnetic resonance angiography. (21)

Glomerular Causes of Hematuria

In immunoglobulin (Ig) A nephropathy, macroscopic hematuria appears concomitantly with infectious illness, most commonly viral respiratory or gastrointestinal in origin. Often, patients with IgA nephropathy have persistent microscopic hematuria between episodes of illness. Some degree of accompanying proteinuria, at least at times of intercurrent illness, is also common. Usually no family history of renal disease is found in these patients. The most common systemic vasculitis in childhood, IgA vasculitis, more widely known as Henoch-Schönlein purpura (HSP), is characterized by palpable purpuric lesions (in the setting of neither thrombocytopenia nor coagulopathy), oligoarticular and transient nondeforming arthritis/arthralgia, abdominal pain, and renal disease. Renal involvement has been reported in up to half of children with HSP, with a tendency toward an older subset that most commonly develops hematuria with or without RBC casts and no or mild proteinuria. (22)(23)(24) Less than 5% of patients with HSP with this mild renal presentation develop chronic kidney disease (CKD) compared with ≥50% of patients with HSP with a more serious initial presentation that is nephritic/nephrotic in nature. (22)(25) Patients with repeated episodes of isolated macroscopic hematuria are also at risk for CKD in the long term. (26) Both IgA nephropathy and IgA vasculitis are considered related diseases and display similar histologic features and IgA deposits.

Alport syndrome (AS) is a hereditary disease with both gross and microscopic hematuria that is associated with high risk of progression to end-stage renal disease (ESRD) even before the fourth decade of life. The inheritance pattern is most commonly X-linked (80% of patients with AS) but may also be autosomal recessive or dominant. The genetic abnormality that characterizes X-linked AS involves the α-5 chain of type IV collagen (COL4A5), and mutations in the *COL4A3* and *COL4A4* genes are responsible for the recessive and dominant forms of AS. Because type IV collagen is found in the ear and eye in addition to the glomeruli, AS is often associated with high-frequency sensorineural hearing loss and ocular abnormalities, including anterior lenticonus. (12) The rate of progression of renal disease depends on the nature of *COL4A* mutations. (12)

Thin basement membrane disease, also known as benign familial hematuria, is an autosomal dominant condition in which patients demonstrate persistent microscopic

TABLE 2. Causes of Hematuria in Children

CONDITION	HEMATURIA/MICRO OR MACRO	PROTEINURIA	HISTORY	EXAMINATION	DIAGNOSTIC EVALUATION
Transient					
Exercise	Micro	+	Hematuria and/or proteinuria after exercise	Noncontributory	Absence of hematuria or proteinuria without exercise
Fever	Micro	+	Hematuria and/or proteinuria with febrile episode	Focal or systemic illness associated	Absence of hematuria or proteinuria after illness resolves
Urinary tract infection or pyelonephritis	Micro or macro	+	Dysuria, urgency, frequency, fever, flank pain, sterile pyuria	Fever, flank or lower abdominal tenderness	Urine dipstick, urine microscopy, urine culture
Trauma/instrumentation	Macro	–	Recent trauma or procedure	Noncontributory or findings related to trauma	Imaging studies
Urethritis	Micro	–	Sexually active	Normal/penile discharge	NAAT for gonorrhea/chlamydia
Bladder calculus/mass	Macro	–	History of nephrolithiasis	+/– Abdominal tenderness	Imaging, 24-h urine metabolic evaluation
Schistosomiasis	Terminal macro	–	Recent travel and contact with fresh water; previous serum sickness–like illness; dysuria, frequency	Decreased urine output	Imaging, PCR of urine or stool
Adenovirus hemorrhagic cystitis	Macro	–	Recent URI signs and symptoms	Active URI signs	Respiratory viral screen including adenovirus
Persistent					
Nonglomerular					
Hypercalciuria	Micro	–	Family history of nephrolithiasis	Noncontributory	High Ca/Cr
Nephrolithiasis	Micro or macro	+/–	Poor daily oral fluid intake, flank pain	Normal/CVA or flank tenderness	High Ca/Cr, imaging, crystals on UA
Nutcracker syndrome	Micro or macro	Up to 15%	Flank pain	Noncontributory	Imaging
Sickle cell trait	Micro	–	Sickle cell trait or anemia	Noncontributory	Hemoglobin electrophoresis
Coagulation disorders	Micro or macro	–	Known disease or family history, bruising, bleeding, petechiae, lethargy	Petechiae, ecchymosis, bleeding	Abnormal clotting profile, CBC count
Polycystic kidney disease	Micro or macro	+	Family history of polycystic kidney disease	Abdominal mass	Ultrasonography, genetic evaluation
Wilms tumor	Micro or macro	+/–	Incidental finding, gross hematuria, abdominal pain, hypertension, fever	Abdominal mass	Ultrasonography
Structural abnormalities of kidney, ureter, bladder (eg, UPJO, UVJO)	Micro	–	Noncontributory, recurrent or first-time UTI, family history of CAKUT	Abdominal mass	Ultrasonography, radioisotope renography

Continued

TABLE 2. (Continued)

CONDITION	HEMATURIA/MICRO OR MACRO	PROTEINURIA	HISTORY	EXAMINATION	DIAGNOSTIC EVALUATION
Glomerular					
IgA nephropathy[a]	Micro or macro	+/–	Concomitant recurrent hematuria with infectious illness, flank pain (rare)	Noncontributory	Normal complements, kidney biopsy
Henoch-Schönlein purpura[a]	Micro/macro	+/–	Nonblanching rash, joint swelling, abdominal pain, and intussusception	Petechial/purpuric rash, joint swelling, hypertension	Normal C3/C4
Alport syndrome[a]	Micro or macro	+/–	Family history, persistent microscopic or episodic macroscopic hematuria; poor school performance	Hearing/visual abnormalities	Genetic evaluation, kidney or skin biopsy
Thin basement membrane disease[a]	Micro or macro	–	Family history, persistent microscopic or episodic macroscopic hematuria	Noncontributory	Nil
Postinfectious glomerulonephritis[a]	Micro or macro	+/–	Recent history of URI or skin infection	Red posterior oropharynx, hypertension, fluid overload	Antistreptolysin O titer, anti-DNase B, throat culture
Hemolytic uremic syndrome[a]	Micro	+/–	Bloody diarrhea, oliguria, history of sick contact or ingestion of uncooked meat	Edema, intravascular fluid depletion, pallor, petechiae	Stool culture for *Escherichia coli* O157:H7

BUN=blood urea nitrogen; Ca/Cr=calcium/creatinine; CAKUT=congenital anomalies of the kidney and urinary tract; CBC=complete blood cell; CVA=costovertebral angle; IgA=immunoglobulin A; NAAT=nucleic acid amplification test; PCR=polymerase chain reaction; UA=urinalysis; UPJO=ureteropelvic junction obstruction; URI=upper respiratory infection; UTI=urinary tract infection; UVJO=ureterovesicular junction obstruction.

[a]Considered to be a serious condition requiring prompt evaluation by/discussion with a pediatric nephrologist.

Adapted from refs 14, 15, and 27.

hematuria but no apparent CKD progression over a lifetime, hence the "benign" designation to the disease. Kidney biopsy may reveal isolated thinning of the glomerular basement membrane on electron microscopy. Although, traditionally, thin basement membrane disease is thought to be benign, the condition is not a homogenous entity and rather has been associated with various genetic mutations. It has been described as the heterozygous form of autosomal recessive AS involving *COL4A3* and *COL4A4* (Alport being the homozygous phenotype); and as giant fibronectin glomerulopathy, C3/CFHR5 glomerulonephritis (GN), immunotactoid GN, and fibrillary GN based on new genetic information. These rare glomerulopathies have been noted to have a not so benign renal outcome, with approximately a 20% to 40% risk of progressing to some stage of CKD. (12)(28)(29)(30)

Postinfectious GN is the most common cause of acute nephritis in children around the world. Children aged 5 to 12 years are at greatest risk. Postinfectious GN has a wide range of presentations, from asymptomatic, microscopic hematuria to full-blown acute nephritic syndrome (red-brown urine, proteinuria, edema, hypertension, and acute kidney injury). Because asymptomatic microscopic hematuria is the most common presentation, obtaining a recent history of group A streptococcal skin (2–6 weeks earlier) or throat (1–2 weeks earlier) infection becomes critical on the initial evaluation to make this diagnosis. When diagnosis is delayed or if disease is more severe, presentation may be characterized by fluid overload status (hypertension, edema, pulmonary edema). Laboratory investigation may reveal low complement protein C3 but normal C4 levels; a low C3 level in postinfectious GN usually resolves by 4 to 6 weeks (31); a low C3 level that persists beyond this time frame may warrant a renal biopsy, especially if there is continued hematuria and/or proteinuria. Children tend to have complete clinical recovery and show resolution of the disease within 1 to 2 weeks. Microscopic hematuria can persist up to 6 months.

Evaluation of Hematuria

Children with 1+ blood on urine dipstick should have a UA with microscopic evaluation of the urine to verify the presence of urinary RBCs and to assess RBC quantity and shape. If RBCs are eumorphic one should consider urinary tract infection, hypercalciuria, genitourinary malformation, and/or familial causes of hematuria (Fig 1).

Isolated microscopic hematuria has a good renal outcome in general, but the lifetime risk of CKD may be higher in certain patients, depending on the specific underlying disease. Microscopic hematuria is generally monitored on a yearly basis but may require more frequent monitoring if associated with macroscopic hematuria and/or proteinuria because these can be associated with worse renal outcome. Furthermore, genetic analysis in the setting of a positive family history of hematuria and/or proteinuria or ESRD has been recommended by several authors for early detection of rare progressive hereditary renal diseases such as giant fibronectin glomerulopathy, C3/CFHR5 GN, immunotactoid GN, and fibrillary GN, which were previously classified under the umbrella of benign familial hematuria. Therefore, these cases of persistent microscopic hematuria might also prompt consideration of subspecialty referral, especially if there is any family history of CKD. (12)

PROTEINURIA

Prevalence

Although not always pathologic, proteinuria is recognized as a marker of kidney damage and is a well-known risk factor for progression to CKD in adults and children. The prevalence of proteinuria on a random urine specimen in otherwise asymptomatic school-aged children and adolescents is approximately 5% to 15% based on multiple large-scale studies. (32) This finding decreases substantially with repeated urine samples. One study examined 4 repeated urine specimens from each of approximately 9,000 children (8–15 years old); 1 of 4 specimens was positive for protein in 10.7% of patients, but only 0.1% had 4 of 4 specimens positive with persistent proteinuria. (33) The specific type of protein excreted in the urine, such as albumin or low-molecular-weight (LMW) proteins, depends on the type of kidney disease. Albuminuria is more strongly associated with CKD as a marker of glomerular disease and is a long-term complication of diabetes and hypertension. In contrast, urinary loss of LMW proteins is more reflective of tubulointerstitial disease. (32) For the purpose of this review, the term *proteinuria* refers to increased urinary excretion of albumin and/or other specific proteins, such as immunoglobulins or LMW proteins.

Definition

Although a small amount of protein in the urine is considered acceptable, proteinuria is defined as protein excretion greater than 100 mg/m^2 per day or more than 0.2 mg protein/mg creatinine (also known as a urine protein/creatinine ratio ([U p/c] >0.2) on a single spot urine collection; in neonates and infants, a higher amount of protein excretion, up to 300 mg/m^2, is allowed. Nephrotic-range proteinuria is defined as greater than 1,000 mg/m^2 per day or greater than 50 mg/kg per day, or a U p/c greater than 2 on a single spot urine collection.

Measurement Methods

Different methods are used to quantify the amount of protein excreted in the urine, with the urine dipstick being the most frequently used by primary care physicians. The dipstick largely detects albumin and does not tend to detect LMW proteins. Ranges can vary depending on the manufacturer; for the purpose of this article, a negative urine dipstick for protein corresponds to a concentration of less than 0.015 g/dL (0.15 g/L) of albumin in the urine, trace corresponds to 0.015 to 0.030 g/dL (0.15–0.30 g/L) of albumin in the urine; 1+ corresponds to 0.030 to 0.100 g/dL (0.30–1.00 g/L) of albumin in the urine; 2+ corresponds to 0.100 to 0.300 g/dL (1.00–3.00 g/L) of albumin in the urine; 3+ corresponds to 0.300 to 1.000 g/dL (3.00–10.00 g/L) of albumin in the urine; and 4+ corresponds to greater than 1.000 g/dL (>10.00 g/L) of albumin in the urine. A false-positive urine dipstick for protein can occur when the urine sample has a high specific gravity (ie, a concentrated urine) or is very alkaline. Contamination with antiseptic agents or iodinated radiocontrast agents can also produce a false-positive result for protein, and as such it is recommended to wait at least 24 hours after a contrast study to test for protein in the urine. (34)

A more accurate method of measuring protein in the urine is by 24-hour urine collection. Adequacy of a 24-hour urine collection may be verified by measurement of urine creatinine, which is approximately 15 to 20 mg/kg ideal body weight in females and 20 to 25 mg/kg ideal body weight in males. (35) However, in infants and children, especially in those who are not toilet trained, this method tends to be difficult to perform accurately. As such, calculation of a U p/c in a random or spot urine sample has become recognized as an acceptable alternative to a 24-hour urine collection for protein, especially in the pediatric population. The U p/c has been shown to be a fairly reliable surrogate for a 24-hour urine collection, especially when tested in the first morning urine specimen. (36)(37) A normal U p/c is less than 0.2 mg protein/mg creatinine in children older than 2 years and less than 0.5 mg protein/mg creatinine in infants and children 6 to 24 months old. (38) Points to consider when measuring protein in this manner include a falsely elevated U p/c when there is not enough creatinine excreted or underestimation of the ratio when there is a very concentrated sample with a high creatinine level in the urine. (39)(40) Our practice is to send a urine sample for U p/c as well as UA, with the expectation that significant proteinuria will be evident on both examinations.

Testing for microalbuminuria is valuable for screening for diabetic nephropathy in the pediatric population. It is highly sensitive to detect very small quantities of albumin in the urine; this test has grown in importance with the epidemic of obesity in the pediatric population. (32)

Qualitative assessment of proteinuria to differentiate glomerular from tubular proteinuria can be performed by measuring β-2 microglobulin, α-1-macroglobulin, lysozyme, and retinol-binding protein. These levels will be 10 to 100 times higher than normal in tubular proteinuria (eg, proximal tubular dysfunction seen in Fanconi syndrome).

Classification

Proteinuria can be classified as transient, orthostatic, and persistent. Transient proteinuria, which can be defined as proteinuria noted on 1 or 2 occasions but not present on subsequent testing, is often seen in the context of fever, exercise, stress, seizures, and hypovolemic/dehydration status. (41) Orthostatic proteinuria is characterized by increased protein excretion in the upright position, which returns to normal when the patient is recumbent. On average, these patients excrete less than 1 g of protein in 24 hours in the upright position, and this normalizes to less than 50 mg in 8 hours of supine position. Orthostatic proteinuria is one of the most common causes of proteinuria in adolescents. (41) It is diagnosed when a first morning urine sample is less than 0.2 mg protein/mg creatinine in the setting of a U p/c greater than 0.2, or positive urine dipstick for proteinuria, in a random urine sample (Fig 2). The pathophysiology underlying orthostatic proteinuria remains poorly understood, but the prognosis has traditionally been thought to be good. Studies from the 1960s to the 1990s on up to 40 to 50 years after the diagnosis of orthostatic proteinuria have reported a benign course for this condition, where mortality is not shown to be greater than the average healthy population with similar demographic characteristics in the absence of other clinical evidence of renal disease. (42)(43)(44)

Based on the mechanism of the proteinuria, persistent proteinuria may be subclassified as glomerular, tubular, or overflow. Glomerular proteinuria refers to an anatomical or functional lesion in the glomeruli that results in an increased filtration of protein across the glomerular capillary wall. Tubular proteinuria is seen when there is an increased excretion of LMW proteins due to interference with proximal tubular reabsorption. Overflow proteinuria refers to an increased excretion of LMW proteins that results from marked overproduction of LMW proteins, leading to a level that exceeds tubular reabsorptive capacity; overflow proteinuria is very rarely seen in children and is not discussed in this review.

Among the most common causes of primary glomerular proteinuria seen in children (Table 3), minimal change disease (MCD) represents one of the most common presentations of idiopathic nephrotic syndrome. It classically presents in children (most between 3 and 9 years of age) as edema, a low albumin level (<2.5 g/dL [25.0 g/L]), proteinuria, and hyperlipidemia in the setting of normal renal function and complement levels, and absence of hypertension and/or gross hematuria. (45) Based on this clinical diagnosis, corticosteroid therapy is recommended without a confirmatory diagnosis by renal biopsy as more than 90% of cases will respond within 4 weeks. (46) Based on the response and frequency of relapses, MCD can be further subclassified. In a case where a patient is found to be corticosteroid resistant or if the clinical/laboratory presentation is different from that described previously herein, a renal biopsy should be considered. On histopathology, MCD glomeruli appear normal under light microscopy but show characteristic effacement of foot processes on electron microscopy. (47)

In teenagers who present with massive proteinuria, or in children with proteinuria who are found to be corticosteroid resistant, one should consider focal segmental glomerular sclerosis (FSGS) in the differential diagnosis. This disorder is named after the typical histologic lesion characterized by some (focal) glomeruli with areas (segmental) of sclerosis

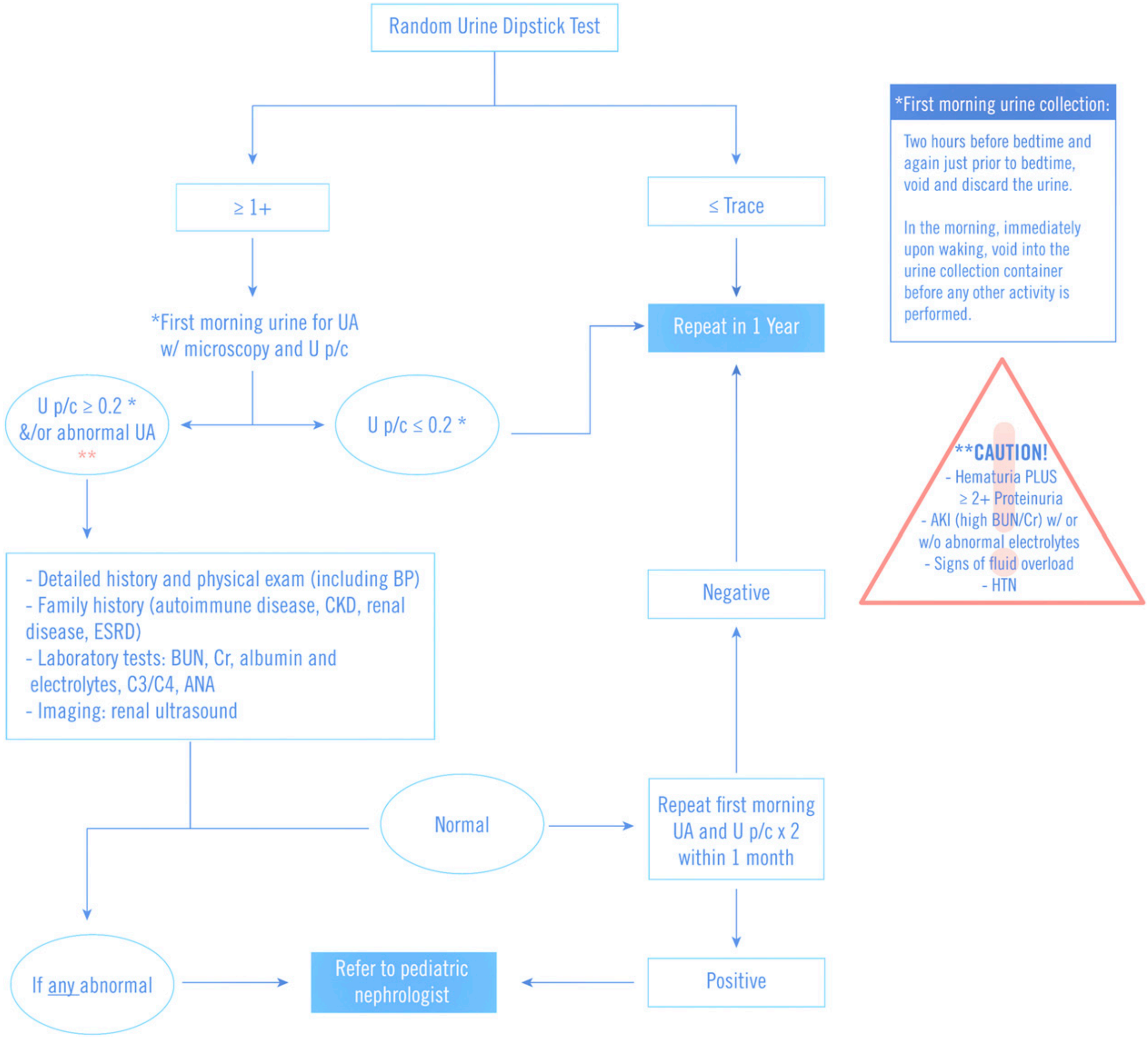
Random Urine Dipstick Test
≥ 1+
≤ Trace
*First morning urine for UA w/ microscopy and U p/c
Repeat in 1 Year
U p/c ≥ 0.2 * &/or abnormal UA **
U p/c ≤ 0.2 *
- Detailed history and physical exam (including BP)
- Family history (autoimmune disease, CKD, renal disease, ESRD)
- Laboratory tests: BUN, Cr, albumin and electrolytes, C3/C4, ANA
- Imaging: renal ultrasound
Negative
Normal
Repeat first morning UA and U p/c x 2 within 1 month
If any abnormal
Refer to pediatric nephrologist
Positive
*First morning urine collection:
Two hours before bedtime and again just prior to bedtime, void and discard the urine.
In the morning, immediately upon waking, void into the urine collection container before any other activity is performed.
**CAUTION!
- Hematuria PLUS ≥ 2+ Proteinuria
- AKI (high BUN/Cr) w/ or w/o abnormal electrolytes
- Signs of fluid overload
- HTN

Figure 2. Approach to a child with asymptomatic proteinuria. Caution items warrant urgent consultation with a nephrologist. ANA=antinuclear antibody; AKI=acute kidney injury; BP=blood pressure; BUN=blood urea nitrogen; C3=complement component 3; C4=complement component 4; Ca/Cr=calcium/creatinine; CKD=chronic kidney disease; ESRD=end-stage renal disease; HPF=high-power field; HTN=hypertension; RBC=red blood cell; UA=urinalysis; U p/c=urine protein/creatinine ratio. (Adapted from refs 14, 41, 48, and 49.)

or scarring, alongside areas of normal glomeruli. A recent study describes FSGS in up to 56% of children younger than 20 years of age (most of the cohort aged 1–11 years) with initial presentation of corticosteroid-resistant nephrotic syndrome. (50) The histopathologic diagnosis of FSGS is notably more prevalent in black patients compared with white patients, which may be related to the higher incidence of apolipoprotein L1 gene in this population. (51)(52)(53) Primary/idiopathic FSGS, where circulating permeability factors are thought to be involved in the pathogenesis, often presents with the classic nephrotic syndrome triad of proteinuria, hypoalbuminemia, and edema in the absence of identifiable risk factors (eg, severe obesity, decreased renal mass [as may be seen in prematurity], viral infection, drugs). Secondary FSGS, on the other hand, usually presents with subnephrotic-range proteinuria in the presence of identifiable risk factors. Several genetic forms of FSGS have been described. Mutations are most commonly described in the nephrin gene (*NPHS1*, which is also responsible for congenital nephrotic syndrome [see later herein]) and the podocin gene (*NPHS2*); both follow an autosomal recessive pattern and usually present in the first year of life. (50)(54)(55) In contrast, autosomal dominant forms of FSGS (such as mutations in alpha-actin-4 or TRPC6) tend to present in adolescence or later in adulthood.

TABLE 3. Persistent Proteinuria

CONDITION	HEMATURIA/ MICRO OR MACRO	PROTEINURIA	HISTORY	EXAMINATION	INVESTIGATIONS TO CONFIRM DIAGNOSIS
Glomerular					
Primary					
Minimal change disease	–/+/Micro	4+	Age 2–10 y, recent viral infection, nephrotic features	Anasarca	U p/c >2.0, low albumin level, hyperlipidemia, thrombocytosis, normal C3/C4
Chronic kidney disease/adaptation due to nephron loss	–/+/Micro	1-4+	History of vesicoureteral reflux or recurrent UTIs; history of urologic abnormalities, prematurity, AKI (Table 1)	Noncontributory	Depending on history, but will likely include chem-10 and cystatin C
Congenital nephrotic syndrome	–/+/Micro	4+	Age <3 mo, prematurity, large placenta, edema at birth or first week of age	Anasarca	Elevated α-fetoprotein in amniotic fluid, U p/c >2.0, low albumin level, hyperlipidemia, normal C3/C4
Focal segmental glomerular sclerosis	–/+/Micro	1-4+	History of corticosteroid-resistant nephrotic syndrome, history of HIV infection	Nephrotic features, hypertension	U p/c >2.0, normal to low renal function, hyperlipidemia, thrombocytosis, normal C3/C4
Immune complex–mediated membranoproliferative glomerulonephritis	–/+/Micro or macro	1-4+	Hepatitis B or C infection, rheumatologic disease, malignancy	Nephrotic or nephritic features	Low C3, low or normal C4, hepatitis serology; depends on underlying cause
C3 glomerulopathy	–/+/Micro	1-4+	History of renal disease in family members	Nephrotic or nephritic features	Low C3, normal C4; U p/c >2.0; normal to low renal function; mutations or antibodies to complement components
MN	–/+/Micro	2-4+	History of corticosteroid resistant NS	Nephrotic features	Primary MN: + antiphospholipase A2 receptor; rule out causes for secondary MN such as hepatitis B or C, HIV, or SLE
Secondary					
Diabetes mellitus	+	1-3+	Polyuria, polydipsia, polyphagia, weight loss	Intravascular depletion	Elevated blood glucose and hemoglobin A_{1C} levels, glucosuria
SLE	+/Micro or macro	1-4+	Fatigue, weakness, multisystem symptoms	Malar rash, joint swelling, fluid overload, hypertension	Pancytopenia, anti-dsDNA, + ANA, high ESR, low C3 and C4

Continued

TABLE 3. **(Continued)**

CONDITION	HEMATURIA/ MICRO OR MACRO	PROTEINURIA	HISTORY	EXAMINATION	INVESTIGATIONS TO CONFIRM DIAGNOSIS
Tubular					
Primary					
Cystinosis	+/Micro	+ (LMW)	Depends on age at onset, visual impairment, delayed puberty, Fanconi syndrome	Hepatosplenomegaly, cystine corneal crystals	Elevated cystine level, concentrating defect, type 2 RTA,[a] *CTNS* gene mutation
Wilson disease	+/Micro	+ (LMW)	Neurologic and behavioral symptoms, liver dysfunction, Fanconi syndrome	Kayser-Fleischer rings, hepatosplenomegaly	Low ceruloplasmin level, elevated liver enzyme levels, type 2 RTA[a]
Lowe syndrome	+/Micro	+ (LMW)	Fanconi syndrome	Cataracts, cognitive impairment, hypotonia	Type 2 RTA,[a] OCRL 1 mutations
Secondary					
Acute interstitial nephritis	–/+/Micro	+	Recent use of NSAIDs, penicillin, quinolones, sulfonamides, cimetidine, cephalosporins, allopurinol	Subclinical, late in disease may have typical features of renal failure; tubulointerstitial nephritis and uveitis, red, painful eye	Urinary WBCs or WBC casts, urine eosinophils, concentrating defect
Acute tubular necrosis	–/+/Micro	+	Recent use of aminoglycosides, cisplatin, NSAIDs, radiocontrast media, amphotericin B. history of circulatory impairment or hypoxia	AKI, oliguria	Elevated BUN and creatinine levels; granular or muddy brown casts on microurinalysis, fraction excretion of sodium >2%
Heavy metal poisoning	–/+/Micro	+	Recent exposure to copper, lead, or mercury	Cognitive or behavioral impairment lead, lead lines along gum margin	Elevated level of toxin
Obstructive uropathy	–/+/Micro	+	Flank or abdominal pain, decreased urine output	Suprapubic mass, oliguria or anuria	Ultrasonography, VCUG, elevated BUN and creatinine levels

AKI=acute kidney injury; ANA=antinuclear antibody; BUN=blood urea nitrogen; ESR=erythrocyte sedimentation rate; HIV=human immunodeficiency virus; LMW=low molecular weight; MN=membranous nephropathy; NSAID=nonsteroidal anti-inflammatory drug; SLE=systemic lupus erythematosus; U p/c=urine protein/creatinine ratio; UTI=urinary tract infection; VCUG=voiding cystourethrogram; WBC=white blood cell.

[a] *Type 2 RTA (renal tubular acidosis, proximal type) often accompanied by glycosuria, aminoaciduria, and LMW proteinuria.*

Adapted from refs 14, 16, 44, 49, 56, and 57.

Congenital nephrotic syndrome (CNS) refers to nephrotic syndrome that appears early in infancy, generally presenting with heavy proteinuria and marked ascites within the first 3 months after birth. In contrast to nephrotic syndrome occurring later in childhood or adolescence, CNS is more commonly associated with genetic mutations, namely, *NPHS1*, followed by *NPSH2*, encoding key components of the slit diaphragm, nephrin and podocin. Congenital nephrotic syndrome can be associated with a history of prematurity (35–38 weeks), low birthweight for gestational age, and large placenta (>25% of birthweight). The significant urinary protein losses result in hypoalbuminemia, hypogammaglobulinemia, and dysregulation of the clotting cascade, which make these children prone to poor nutritional status and growth, as well as a heightened incidence of bacterial infections and thromboembolic events. (58) Genetic cause has been described in up to 70% of infants presenting in the first 3 months of age and up to 50% of those aged 4 to 12 months. (50)(59) Children with CNS, with or without identified genetic mutations, are usually corticosteroid resistant and have a poorer prognosis. As part of nongenetic causes of CNS, one should consider prenatal and perinatal infections (TORCH infections such as rubella, toxoplasmosis, congenital syphilis, human immunodeficiency virus, cytomegalogvirus, etc), mercury intoxication, maternal systemic lupus, and neonatal alloimmunization antineutral endopeptidase; most of these causes have a specific treatment. (52)(60) Although care remains complex and the prognosis remains guarded for infants with nephrotic syndrome, improved protein supplementation, adequate nutritional support, and renal replacement therapy (if needed) may allow the child with CNS to grow big enough to become a candidate for renal transplant. (58) These advances in medical care offer the patient with CNS an overall improved prognosis.

Previously discussed acute postinfectious GN and HSP (see previously herein) are known to be secondary causes of glomerular proteinuria (Table 3). This category of disease also includes lupus nephritis, which is the term used to describe the renal (usually glomerular) involvement of systemic lupus erythematosus (SLE). Systemic lupus erythematosus is a chronic autoimmune disease that can involve any organ system, and its childhood onset is known to have a more severe course compared with adult onset. (61) Renal disease is present in 50% to 75% of children with SLE and is one of the leading causes of morbidity and mortality. (61) According to current histopathologic classification of SLE, most would consider class I (minimal mesangial) and class II (mesangial proliferative) mild lesions. Class III (focal proliferative) and class IV (diffuse proliferative), in contrast, are more severe lesions with high rates of progression to ESRD; unfortunately, class III and IV are also the most common lesions found in children. (62) Aggressive immunotherapy in these cases is recommended to mitigate the associated inflammatory damage. (63)(64) Class V (membranous lupus nephritis) on its own is considered less severe than class III and IV, although it most commonly presents in conjunction with class III or IV. The clinical presentation of SLE does not always correlate well with the severity of the histopathologic findings, and, because there is no reliable biomarker available that correlates well with disease activity, a renal biopsy should be considered when GN is suspected, including in the case of persistent mild proteinuria. (62)(65) All children with SLE should have close monitoring of blood pressure, serum creatinine level, proteinuria, and hematuria because renal disease can also be representative of disease flares, even after remission. (62)(65) For patients with previous active SLE nephritis, follow-up is recommended every 3 months. (66)

In children, as in adults, nephrotic-range proteinuria is a serious condition on its own that can be associated with myriad complications: increased risk of infections are seen as defects in humoral immunity, making these patients more prone to encapsulated bacterial infections; thromboembolic events from decreased levels of protein S, plasminogen, and antithrombin III and increased levels of fibrinogen and factors V and VIII; renal failure from recurrent episodes of acute kidney injury and hypovolemia; and anasarca, the most extreme form of fluid maldistribution, which presents with massive generalized edema, large pleural effusions, and ascites. (47) Any or all of these complications can negatively impact the clinical course.

Although proximal tubular loss of LMW proteins may be significant, isolated urine protein loss of this kind is not associated with the body swelling noted in nephrotic syndrome. Tubular proteinuria most often appears as a result of injury to the proximal tubule and in the pediatric population is more commonly secondary rather than primary in nature. Tubular damage, often induced by various drug exposures or circulatory compromise, results in impaired ability to reabsorb the LMW proteins, which are normally filtered by the glomerulus and reabsorbed by the proximal tubule. Although secondary rather than primary causes of tubular proteinuria are more likely to be encountered in children (such as acute tubular necrosis and acute interstitial nephritis), one should take note of a few primary causes that may be considered, including but not limited to cystinosis, polycystic kidney disease, Wilson disease, and mitochondrial disorders (Table 3).

Note that persistent proteinuria is associated with CKD. Proteinuria that is persistent may be the first sign of glomerular damage or loss of renal function. It has long been established that the degree of proteinuria is associated with progression of CKD. (35) Not only does protein serve as an indicator of renal damage, but it is also recognized as a perpetrator of ongoing renal damage. (35)(67)(68) As such, children who present with persistent proteinuria should undergo evaluation of renal function, and a thorough history detailing any significant illnesses or prenatal or perinatal events is essential (including but not limited to items listed in Table 1) to help determine possible causes.

Evaluation of Proteinuria

Patients with a positive urine dipstick (≥1+) of protein should have a complete UA and quantification of proteinuria with a spot U p/c, preferably in a first morning urine sample. This sample is best obtained by completely emptying the bladder before going to sleep (discarding that urine) and collecting the urine on awakening, before any other activity is performed. (48)(49) No further evaluation is necessary if the first morning urine sample has a normal U p/c of 0.2 or less (Fig 2) because the most likely diagnosis is orthostatic proteinuria and historically is not associated with long-term sequelae. Still, some pediatric nephrologists would advise repeating a first morning void on a yearly basis in patients who continue to demonstrate proteinuria. (48) Further evaluation is warranted if the first morning U p/c is greater than 0.2; these patients should undergo renal ultrasonography, serum creatinine, albumin, cholesterol and electrolytes, and C3/C4 and antinuclear antibodies, especially in the setting of a positive family history of autoimmune disorders or renal disease (Fig 2). (35)(48)(49) At this point, referral to a pediatric nephrologist may be indicated.

Being able to differentiate between temporary or benign proteinuria and proteinuria associated with a more serious condition can be challenging. Persistent proteinuria should not be overlooked because it is well-known to be associated with CKD. At the same time, the primary care provider should be aware that most adolescents who are found to have proteinuria on a screening UA do not have true renal disease and the proteinuria will resolve on repeated testing. (33) Confirming proteinuria that is or is not orthostatic in nature can and should be determined in a timely manner, as prompt referral to a pediatric nephrologist may be needed for those in whom a more serious condition is being considered. By the same token, declining further evaluation of transient and orthostatic proteinuria in an asymptomatic patient can potentially lead to avoidable family and patient anxiety, as well as unnecessary investigations and expenses.

CONCLUSION

Hematuria and proteinuria are findings that can be of concern to both clinicians and families. Fortunately, in the great majority of cases, repeated studies or further evaluation will reveal no abnormalities and little or no need for further evaluation. If hematuria and/or proteinuria is confirmed, a detailed history along with investigation for extrarenal symptoms, high blood pressure, and abnormal renal chemistries will be helpful when deciding who may be followed in the primary care office versus who to refer to nephrology for further evaluation, and how soon to refer. Further studies, including additional laboratory work, radiologic imaging, and percutaneous renal biopsy, may be undertaken by the consulting nephrologist to elucidate the cause of the urinary abnormality and to guide management.

Summary

- Based on some research evidence as well as consensus, hematuria or proteinuria that persists on repeated testing warrants additional evaluation, and, depending on history along with initial evaluation in the primary care office, may warrant referral to a pediatric nephrologist for further management. (12)(15)(35)(48)
- Based on some research evidence and expert opinion, microscopic hematuria that is associated with macroscopic hematuria and/or proteinuria warrants more urgent referral to a pediatric nephrologist because these signs can be associated with worsened renal outcome. (11)(12)
- Based on some research evidence as well as consensus, the urine protein/creatinine ratio has been shown to be a fairly reliable surrogate for a 24-hour urine collection, especially when tested in the first morning urine specimen. (35)(36)(37)
- Based on observational studies, the long-term prognosis of orthostatic proteinuria is generally benign. (42)(43)(68)
- Based on some research evidence as well as consensus, persistent proteinuria is an indicator of renal damage and is also recognized as a perpetrator of ongoing renal damage. (35)(67)(69)

References for this article are at http://pedsinreview.aappublications.org/content/39/12/573.

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1. A 16-year-old boy is brought to your office by his parents on a Monday morning because he noted his urine appeared red in color. He is known to you. He has a history of participating in numerous high-risk behaviors in the previous year, including binge drinking and ingestion of various drugs as well as accepting eating challenges. He discloses to you that he had some recent upper respiratory infection symptoms and that he had been partying with his friends over the weekend. His physical examination does not reveal any specific abnormalities. His blood pressure is 125/65 mm Hg. A urinalysis (UA) shows reddish urine. The urine dipstick is 3+ positive for blood but negative for protein. The spun sediment performed by the laboratory shows only some granular casts but no red blood cells (RBCs). Which of the following diagnoses most explains these findings in this patient?
   A. Acute postinfectious nephritis.
   B. Acute liver injury.
   C. Acute muscle injury.
   D. Immunoglobulin A nephritis.
   E. Paprika ingestion.
2. A 7-year-old boy is brought to your office by his parents with acute onset of brown-colored urine, vague malaise, and mild periorbital edema. He is otherwise healthy, with a negative medical history. His family history is negative for renal disease. His blood pressure is 130/75 mm Hg. His physical examination shows no abnormalities except for mild periorbital edema. Results of his laboratory studies immediately available include a serum sodium level of 140 mEq/L (140 mmol/L), potassium level of 4.0 mEq/L (4.0 mmol/L), and creatinine level of 0.4 mg/dL (35.4 μmol/L). His UA shows a specific gravity of 1.010, pH 6, 3+ blood, 1+ protein, and more than 100 RBCs per high-power field with few RBC casts. Which of the following is the most appropriate next step in the diagnosis of this patient?
   A. A 24-hour urine collection for protein.
   B. A renal biopsy.
   C. C3 and C4 complement levels.
   D. Genetic testing for renal disease.
   E. Serum immunoglobulin A level.
3. A 10-year-old girl undergoes routine periodic screening for proteinuria because she was born at 28 weeks' gestation and had umbilical catheters placed. She has subsequently grown and developed well and is currently healthy. Which of the following would be a reassuring screening result (that would indicate no further testing at this time)?
   A. A UA that shows specific gravity less than 1.005, pH 6, and 1+ protein.
   B. A UA that shows specific gravity 1.030, pH 8, and 2+ protein.
   C. A urine protein/creatinine ratio (U p/c) of 0.1.
   D. A U p/c of 1.0.
   E. A U p/c of 2.5.
4. A 15-year-old girl is brought to the clinic by her parents for a routine school physical. A routine UA, performed only because her school physical required it, shows a specific gravity 1.010, pH 6, 2+ protein, no blood, and no white blood cells (leukocyte esterase). She is a healthy athlete with a normal medical history and a negative family history for renal disease. She returns after soccer practice the following day and her repeated UA shows very similar results. Which of the following is the best next step in the evaluation of the proteinuria in this patient?

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A. Do a 24-hour urine collection for protein quantitation.
B. Obtain a first morning urine sample and send for U p/c quantitation.
C. Order no further studies, sign her form, and reassure her that she's fine.
D. Refer to pediatric nephrology for renal biopsy.
E. Send today's specimen for U p/c quantitation.

5. A 3-year-old boy is brought to the pediatrician's office by his parents with a 2-day history of increasingly noticeable facial and pedal edema. He is otherwise well and playing actively in the office. He is fully immunized and has a completely negative medical history and a family history that is negative for renal disease. His physical examination shows blood pressure 88/56 mm Hg, mild periorbital edema, and edema of his feet and legs. The remainder of the examination is otherwise normal. A purified protein derivative (PPD) skin test is placed and an initial laboratory evaluation is performed, and the results of both are pending. The pediatrician's office is located in a rural area where access to a pediatric nephrologist is not easily available. Which of the following clinical and laboratory findings in this patient would prompt an immediate referral to a pediatric nephrologist rather than initiating treatment by his pediatrician?

A. Mild ascites on physical examination.
B. Serum albumin level of 1.2 g/dL (12.0 g/L) (reference range, 3.5–4.5 g/dL [35.0–45.0 g/L]).
C. Serum cholesterol level of 350 mg/dL (9 mmol/L) (reference range, <190 mg/dL [<5 mmol/L]).
D. Serum C3 complement level of 24 mg/dL (reference range, 93–120 mg/dL).
E. U p/c of 3.0.

The Adolescent with Menorrhagia: Diagnostic Approach to a Suspected Bleeding Disorder

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Practice Gaps

1. To deliver comprehensive care to the adolescent with menorrhagia, clinicians should recognize patterns of menstrual loss that are atypical of that associated with physiologic hormonal changes. There remains a need for consideration of possible underlying bleeding diatheses when screening the adolescent with heavy menstrual bleeding.
2. Clinicians should be aware of the treatment modalities available to the adolescent with menorrhagia and an underlying bleeding disorder and understand when referral to a hematologist is indicated.

Objectives After completing this article, readers should be able to:

1. Define menorrhagia.
2. Use validated screening tools to identify menorrhagia.
3. Identify cases of menorrhagia in the adolescent that warrant further hematologic evaluation based on predictors noted on history and physical examination.
4. Review the most common bleeding disorders associated with menorrhagia in the adolescent and the diagnostic approach to each disorder.
5. Identify the hormonal and hematologic treatment modalities available for use in the adolescent with menorrhagia and understand the limitations of using each treatment in this age group.
6. Recognize when a referral to a pediatric hematologist/oncologist is indicated.

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ABBREVIATIONS

ACOG	American Academy of Obstetrics and Gynecology
COCP	combined oral contraceptive pill
DDAVP	1-deamino-8-D-arginine vasopressin
FVIII	factor VIII
FIX	factor IX
GnRH	gonadotropin-releasing hormone
HMB	heavy menstrual bleeding
LNG-IUS	levonorgestrel-releasing intrauterine system
LTA	light transmission aggregometry
PBAC	pictorial bleeding assessment calendar
PFD	platelet function defect
TA	tranexamic acid
vWD	von Willebrand disease
vWF	von Willebrand factor

OVERVIEW

Adolescent girls and young women often seek medical attention because of menorrhagia, or heavy menstrual bleeding (HMB). Menorrhagia is defined as menstrual bleeding lasting for more than 7 days, sanitary product use greater than

7 per day, and greater than 80 mL of blood loss per menstrual cycle. (1) Estimated prevalence may be as high as 37%. (2)(3) Menorrhagia can be a significant issue for young women at a time of life characterized by dramatic physical and psychological changes. Patients may not discuss HMB with their health-care provider due to a skewed perception of what constitutes normal menstrual bleeding, particularly if other family members have the same menstrual pattern. In 2006, the American College of Obstetricians and Gynecologists (ACOG), in association with, the American Academy of Pediatrics, issued a committee consensus report emphasizing the need for clinicians to not only recognize patterns of normal and abnormal menstruation but also to thoroughly evaluate the adolescent girl with abnormal bleeding.

In the first few years after menarche most cases of abnormal bleeding in adolescent girls can be attributed to anovulatory cycles and the immaturity of the hypothalamic-pituitary-ovarian axis. However, this dysfunctional uterine bleeding is a diagnosis of exclusion. Menorrhagia should be investigated. Although it may be comforting to parents, patients, and physicians that most cases of adolescent HMB can be considered physiologically normal, clinicians must pursue other diagnoses that may significantly affect long-term health outcomes and quality of life. Menorrhagia is well recognized as a common bleeding manifestation in women, with a documented inherited bleeding disorder. However, in adolescents without a known personal or family history, the potential link between HMB and a coagulopathy is sometimes forgotten. If an underlying bleeding disorder is considered, the diagnostic evaluation becomes much more extensive, involving the input of a pediatric hematologist. Adolescent girls with inherited bleeding disorders are more likely to have menorrhagia and are more likely to develop iron deficiency anemia, a need for blood transfusions, endometriosis, and hemorrhagic ovarian cysts. They may be at increased risk for miscarriage and postpartum hemorrhage. (4) Fifteen percent to 25% of women with iron deficiency anemia are found to have an undiagnosed bleeding disorder. (5) This statistic underscores the importance of a thorough evaluation performed earlier rather than later. The public health impact is significant. Diagnosing a bleeding disorder improves management, especially when menorrhagia has been inadequately controlled by standard hormonal interventions. In this article, we provide a review of the most common inherited bleeding disorders associated with menorrhagia in the adolescent. We provide an outline for diagnostic evaluation and an overview of current management strategies available for this age group.

EPIDEMIOLOGY OF BLEEDING DISORDERS IN ADOLESCENTS WITH MENORRHAGIA

An estimated 20% of American women with menorrhagia have an underlying bleeding disorder (approximately 2.5–3 million American women). (1) Historically, the most common inherited bleeding disorder is von Willebrand disease (vWD), with an estimated population prevalence of 1% to 2%, regardless of sex, race, or ethnicity. (6) Von Willebrand disease has increased prevalence in women with menorrhagia, particularly white women, with estimates as high as 10% to 20%. (5) Platelet function defects (PFDs) account for the next most common bleeding disorder in women and girls with HMB, with an estimated prevalence of 4% to 44%. (7) As recognition of and ability to diagnose PFDs improve, there is evidence that these defects may be as common as vWD. (7) Other less common bleeding disorders include mild hemophilia A or B (formerly referred to as symptomatic carrier states) and rare coagulation factor deficiencies. The prevalence of menorrhagia in women with bleeding disorders is high. Menorrhagia affects 32% to 100% of women with vWD, up to 51% of women with platelet dysfunction, 10% to 57% of women with symptomatic hemophilia, and 35% to 70% of women with rare factor deficiencies. Additional uncommon disorders associated with menorrhagia include plasminogen activator inhibitor-1 deficiency, connective tissue disorders (such as Ehlers-Danlos syndrome), and hereditary hemorrhagic telangiectasia.

SCREENING FOR BLEEDING DISORDERS

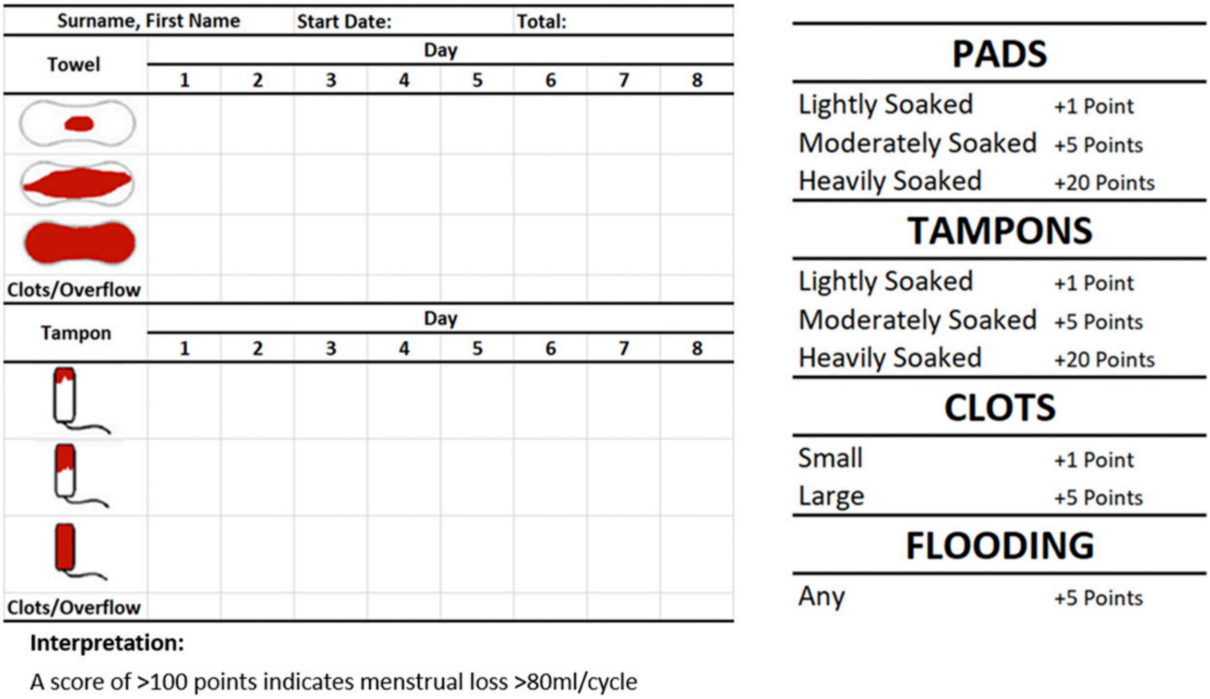
The Healthy People 2020 initiative in the United States included, among its targets, increasing the proportion of physicians who refer for further evaluation of women and girls with symptoms suggestive of an inherited bleeding disorder. (8)(9) Menorrhagia in early adolescence is commonly reported in women with bleeding disorders, often associated with acute hemorrhage and severe anemia requiring hospitalizations and blood transfusions. This typically occurs within the first few years after menarche. (4)(10) Menorrhagia was common in affected female members of the family 'S' of the Aland Islands, first described by Dr. Erik von Willebrand in the 1920s. His index case, Hjordis, bled to death with her fourth menstrual period at 14 years old. (11)(12) Several studies have highlighted the need to evaluate women for an underlying bleeding disorder if they develop HMB throughout their menstrual life. The most recent ACOG guidelines state that health-care providers should screen all adolescents with menorrhagia for bleeding disorders. (8)(13) Quantifying menstrual bleeding can be challenging in clinical practice. Warner et al (14) identified characteristics of the menstrual bleed that are strong predictors of blood loss greater than 80 mL per cycle: flooding (soaking a pad or tampon in less than an hour) and/or impairment of daily activities with most periods, soaking through night clothes, passing clots greater than 1 inch in diameter, and low serum ferritin level. One proposed method to objectively quantify menstrual blood loss includes the use of a pictorial bleeding assessment calendar (PBAC) (Fig 1). (15)(16) The PBAC score has been validated in women with greater than 80% sensitivity and specificity for scores greater than 100. A menstrual score greater than 100 was associated with blood loss of greater than 80 mL. (15) The PBAC score is simple to use and can be readily incorporated into the initial history. A thorough bleeding history documents easy bruising or bleeding with minor injuries, a history of frequent or difficult-to-control epistaxis, or excessive bleeding after surgeries such as tonsillectomy or dental extractions. A coagulopathy is suggested by iron deficiency anemia, a history of blood transfusions, a family history positive for a diagnosed bleeding disorder, HMB, early hysterectomy, or challenges with bleeding during or after childbirth. (17)

Pertinent physical findings include skin bruising, petechiae, ecchymoses, and pallor, although the absence of these features does not exclude a bleeding disorder. (15)

INHERITED BLEEDING DISORDERS ASSOCIATED WITH MENORRHAGIA

Von Willebrand Disease

Von Willebrand disease is the most common bleeding disorder identified in women with HMB. It affects 1% to 2% of the general population (6) and 3% to 36% of girls with menorrhagia. (4)(15) Von Willebrand factor (vWF) is a large glycoprotein synthesized by megakaryocytes and endothelial cells. It is stored in the Weibel-Palade bodies in endothelial cells and in α-granules of platelets. It is released into the circulation on stimulation by endothelial cell damage. (11)(18) It exists in plasma as a multimeric dimer configuration ranging in size from small (500 kD) to very large (>10,000 kD) high-molecular-weight multimers. (19) Its function in primary hemostasis is to promote platelet adhesion to the subendothelium at the site of vascular injury. High-molecular-weight vWF multimers adhere to platelets better than do small ones. Also, vWF participates in platelet-platelet interactions and, along with fibrinogen, promotes thrombus growth and stabilization. (19) It has a role in secondary hemostasis, serving as a carrier protein for



Surname, First Name	Start Date:				Total:			
Towel	Day							
	1	2	3	4	5	6	7	8
Clots/Overflow								
Tampon	Day							
	1	2	3	4	5	6	7	8
Clots/Overflow								

PADS

Lightly Soaked	+1 Point
Moderately Soaked	+5 Points
Heavily Soaked	+20 Points

TAMPONS

Lightly Soaked	+1 Point
Moderately Soaked	+5 Points
Heavily Soaked	+20 Points

CLOTS

Small	+1 Point
Large	+5 Points

FLOODING

Any	+5 Points

Interpretation:

A score of >100 points indicates menstrual loss >80ml/cycle

Figure 1. Pictorial bleeding assessment calendar (PBAC). Adapted with modifications from Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol.* 1990;97(8):734–739. (16)

coagulation factor VIII (FVIII), protecting it from early proteolytic degradation, and increasing its half-life by 5- to 10-fold. (19) A quantitative deficiency or qualitative abnormality of vWF results in vWD. Von Willebrand disease is classified as type 1 or type 3, which describe partial and near-complete quantitative deficiencies of vWF, respectively, and as type 2, which is characterized by various qualitative defects. (18) Type 1 disease, an autosomal dominant disorder, accounts for 70% to 80% of all cases of vWD. (18)(20) Type 2 disease encompasses subtypes 2A, 2B, 2M, and 2N, which, due to mutations in the vWF gene, cause abnormalities in the interactions between vWF and its ligands. (18) Subtypes are determined by assessment of vWF multimers, measures of interaction of vWF protein with platelets, and measures of FVIII levels. (18) Qualitative or quantitative deficiencies of vWF may manifest as mucocutaneous bleeding: epistaxis, bruising without recognized trauma, gastrointestinal bleeding, oropharyngeal bleeding after brushing or flossing, and prolonged bleeding after trauma and surgery. (18)(20) Severe deficiencies, as in type 3, may also present with hemarthroses and deep muscular hematomas, similar to that seen in hemophilia A or B. (20) Women are disproportionately affected because of menstruation and childbirth. Menorrhagia is the most prevalent symptom in women with vWD (6) and may often be the only symptom in mild type 1 disease. Women with vWD more often bleed through protection and report a longer duration of bleeding compared with controls. They are more likely to develop anemia than women without a bleeding disorder. (6) Severe menorrhagia resulting in blood transfusion was reported in 7% to 22% of women with type 1 vWD. (6)

There is no single definitive test that confirms the diagnosis of vWD. The Table highlights the panel of tests to be requested when there is suspicion of underlying vWD.

An activated partial thromboplastin time will often be normal in vWD because most patients with type 1 disease can maintain adequate FVIII levels. Thrombocytopenia may be seen in type 2B vWD. A complete blood cell count may also show a microcytosis, suggestive of iron deficiency anemia. Initial vWF assays should include vWF antigen, ristocetin cofactor activity, and FVIII assays. (15)(12) The normal level of vWF antigen is generally accepted to be between 50 and 200 IU/dL. (20) A vWF antigen level less than 50 IU/dL is considered to be low and when associated with bleeding is usually diagnostic, although false-positives can occur. A diagnostic dilemma can exist because there can be considerable variation in vWF levels in any individual at any given time. Protein assays may be affected by genetic, physiologic, and pharmacologic factors. The vWF protein is an acute phase reactant. Levels of VWF and FVIII may rise acutely with infection, inflammation, vigorous exercise, hyperthyroidism, and increased levels of estrogen during pregnancy or with the use of hormonal contraceptives. (4) (12) Even the stress associated with laboratory draws can increase protein levels. (4) It is well known that individuals with blood group type O exhibit a 20% decrease in vWF levels compared with individuals with blood type A or B. (21)

Levels of vWF have been shown to vary during the menstrual cycle, although this is not well defined. Limited evidence suggests that levels drawn on days 1 to 4 of the menstrual cycle are least likely to be affected by endogenous hormones. (4) Repeated testing is often necessary to establish or exclude the diagnosis and should be considered if the degree of bleeding and the family history are suggestive of disease. Ideally, on-site sample collection and real-time analysis of samples should be performed to avoid sample degradation and subsequent false-positive results. (12) Interpretation of abnormal laboratory test results is best performed with a hematologist.

Genetic testing for vWD is technically challenging. Von Willebrand factor is a very large polymorphic gene that spans 178 kb of DNA, contains 52 exons, and has more than 300 single nucleotide polymorphisms. (20) This makes gene sequencing difficult and of relevant clinical utility in only very specific situations. For example, identifying large deletions in patients with vWD type 3 suggests an increased risk of developing neutralizing antibodies and anaphylactic reactions on treatment. (18) Identifiable mutations are useful for prenatal diagnosis or carrier analysis. (20) Genetic testing may also be justified if molecular diagnosis will help guide treatment, such as for types 2N and 2B. In these variants, mutations are usually clustered in specific areas of the gene, making sequencing and interpretation less difficult. (18)

Inherited PFDs

Platelet function disorders are increasingly recognized as an underlying etiology of unexplained menorrhagia in adolescents. A retrospective review of medical records performed by Amesse et al (22) identified menorrhagia in 41% of adolescents with a documented PFD. Philipp et al (23) found that in a cohort of multiracial women 17 to 55 years old with previously unexplained menorrhagia, platelet dysfunction was more common than vWD. In this study, compared with white women, black women were more likely to have a PFD associated with menorrhagia. (23) This supports testing for PFDs in adolescents with menorrhagia and a negative evaluation for vWD, especially if the patient is of African descent. Platelet function defects encompass a heterogeneous cluster of disorders that may not be detected until

TABLE. Laboratory Panel for vWD

DIAGNOSTIC TEST	FUNCTION	TYPE OF VWD 1: PARTIAL QUANTITATIVE DEFICIENCY	2A: QUALITATIVE DEFICIENCY WITH ABSENCE OF HIGH- AND INTERMEDIATE-WEIGHT VWF MULTIMERS	2B: QUALITATIVE DEFICIENCY WITH INCREASED AFFINITY FOR PLATELET GLYCOPROTEIN IB; ASSOCIATED WITH MILD THROMBOCYTOPENIA	2M: QUALITATIVE VARIANT WITH DECREASED PLATELET-DEPENDENT VWF ACTIVITY	2N: QUALITATIVE VARIANT WITH DECREASED AFFINITY FOR FVIII	3: COMPLETE DEFICIENCY OF VWF
vWF antigen	Measures the concentration of vWF protein in the plasma	↓	↓ or N	↓	↓	N	↓↓↓
vWF ristocetin cofactor activity	Quantitates agglutination of platelets after addition of ristocetin to plasma (function of vWF activity) A ratio of vWF ristocetin cofactor to vWF antigen differentiates between quantitative and qualitative defects • A ratio >0.6 is seen in quantitative defects (vWD types I and 3) • A ratio <0.6 is seen in qualitative defects (vWD type 2)	↓	↓ ↓	↓ ↓	↓	N	↓↓↓
FVIII assay	Measures the concentration of FVIII in plasma; individuals with type 1 or type 2 may have lower levels of FVIII concentrate	↓ ↓	↓ or N	↓ or N	↓ or N	↓ ↓	↓ ↓ ↓
vWF multimers	High-molecular-weight multimers are the most hemostatically active; distribution of multimer sizes in patient plasma will affect hemostatic phenotype	N	↓ ↓	↓	N	N	↓ ↓ ↓
Ristocetin-induced platelet aggregation	Quantitates platelet aggregation at varying concentrations of ristocetin in the presence of patient-rich plasma	↓ or N	↓	↑	↓	N	↓ ↓ ↓
Type and screen	ABO blood group affects vWF levels and influences interpretation						

FVIII=factor VIII; N=normal; vWD=von Willebrand disease; vWF=von Willebrand factor.

after a bleeding event. Platelets aid in clot formation by adhering to the exposed subendothelium at the site of vascular damage. Platelets subsequently become activated and secrete the contents of intracellular granules, which creates a cascade of adhesion, aggregation, and clot formation. Disorders of platelet function can take place at any step in the cascade, although these steps are so closely intertwined that the classification of platelet function disorders by any single system is challenging. A proposed classification scheme is provided in Fig 2. Platelet defects may be inherited or acquired. Acquired disorders are commonly seen with medications (such as nonsteroidal anti-inflammatory drugs, penicillin antibiotics, and anticonvulsants), immune-mediated disorders, and chronic illnesses such as uremia and liver disease. (7) The most common inherited disorders include dysfunctional adhesion as in Bernard-Soulier syndrome, which is due to a defect of glycoprotein Ib, and Glanzmann thrombasthenia, due to defective glycoprotein IIb/IIIa. These disorders are considered major inherited PFDs and can be associated with significant menorrhagia. (7)(24) Defects of platelet granules, known as storage pool disorders, include α-granule disorders such as gray platelet syndrome and abnormalities in dense granules, as seen in Chediak-Higashi syndrome. Inherited microthrombocytopenia can be seen in Wiskott-Aldrich syndrome. These platelet defects may manifest a mild to

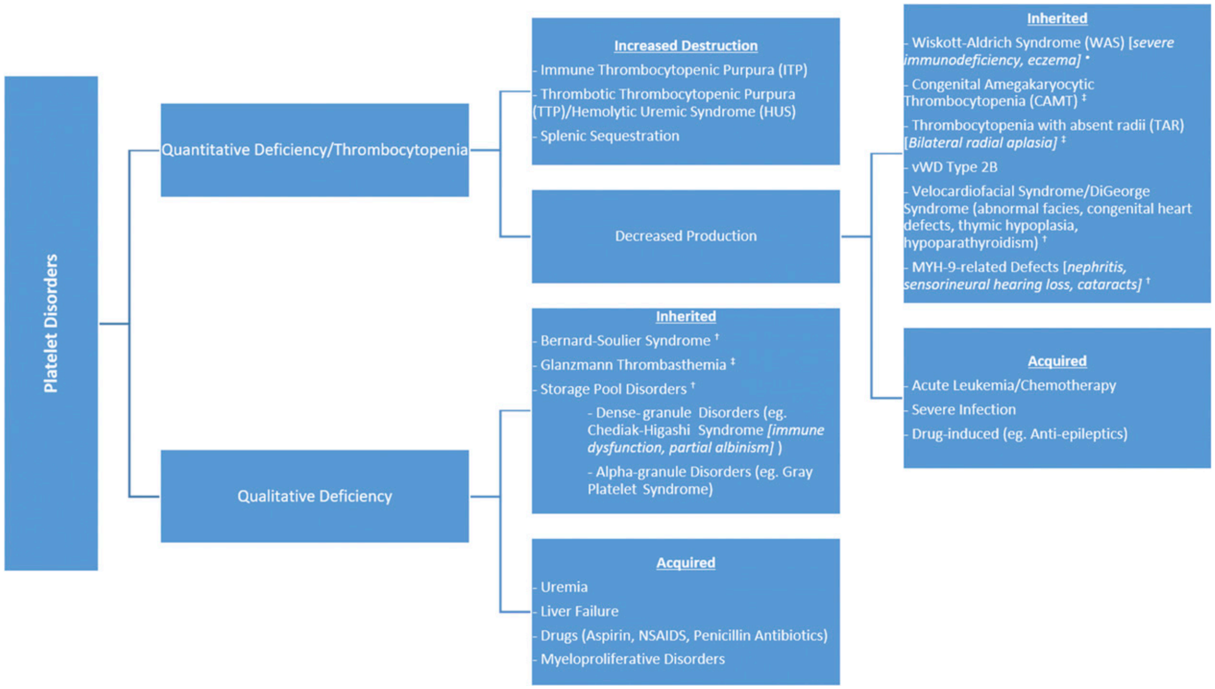

Platelet Disorders
Quantitative Deficiency/Thrombocytopenia
Qualitative Deficiency
Increased Destruction
- Immune Thrombocytopenic Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)/Hemolytic Uremic Syndrome (HUS)
- Splenic Sequestration
Decreased Production
Inherited
- Wiskott-Aldrich Syndrome (WAS) [severe immunodeficiency, eczema] •
- Congenital Amegakaryocytic Thrombocytopenia (CAMT) ‡
- Thrombocytopenia with absent radii (TAR) [Bilateral radial aplasia] ‡
- vWD Type 2B
- Velocardiofacial Syndrome/DiGeorge Syndrome (abnormal facies, congenital heart defects, thymic hypoplasia, hypoparathyroidism) †
- MYH-9-related Defects [nephritis, sensorineural hearing loss, cataracts] †
Acquired
- Acute Leukemia/Chemotherapy
- Severe Infection
- Drug-induced (eg. Anti-epileptics)
Inherited
- Bernard-Soulier Syndrome †
- Glanzmann Thrombasthemia ‡
- Storage Pool Disorders †
- Dense-granule Disorders (eg. Chediak-Higashi Syndrome [immune dysfunction, partial albinism])
- Alpha-granule Disorders (eg. Gray Platelet Syndrome)
Acquired
- Uremia
- Liver Failure
- Drugs (Aspirin, NSAIDS, Penicillin Antibiotics)
- Myeloproliferative Disorders

Figure 2. Classification of platelet disorders. This proposed scheme for the classification of platelet disorders includes characteristic features associated with some platelet disorders. †Large-sized platelets. •Small-sized platelets. ‡Normal-sized platelets. vWD=von Willebrand disease.

moderate bleeding phenotype and can be associated with HMB. In the MYH-9 group of disorders, defects of the platelet cytoskeleton result in macrothrombocytopenia and platelet dysfunction. These disorders can cause severe menorrhagia and other mucocutaneous bleeding symptoms, usually in association with sensorineural hearing loss and renal disease. (7)(25)

Evaluation of a potential platelet disorder begins with a platelet count and peripheral smear. Macrothrombocytopenia, characteristic of Bernard-Soulier syndrome and other giant platelet syndromes, or small platelets, characteristic of Wiskott-Aldrich syndrome, may be obvious by light microscopy.

Platelet aggregometry is the gold standard investigation for PFDs and is usually ordered once vWD and thrombocytopenia have been ruled out. Tests of aggregometry have widely replaced bleeding time. Light transmission aggregometry (LTA), the most widely used method, measures light conduction through plasma thick with platelets; light conduction increases as platelets aggregate in the presence of specific agonists. (7) The test measures the rate and the maximal height of the aggregation response, known as the maximal aggregation. Agonists most commonly used are collagen, adenosine-5'diphosphate, arachidonic acid, and epinephrine. (7) Nonsteroidal anti-inflammatory drugs, antiplatelet agents such as aspirin and clopidogrel, antihistamines, and some antibiotics (β-lactam antibiotics, sulphonamides) may interfere with platelet aggregation. (7) The general life span of circulating platelets is 10 days. These medications should be held for at least 7 to 10 days before having LTA performed. (7) Combined oral contraceptive pills (COCPs) may also affect platelet aggregation; however, many patients require oral contraceptives to manage HMB. Experts recommend performing LTA during a placebo week. Repeated testing is recommended before a diagnosis of platelet dysfunction is confirmed or refuted. Philipp et al (23) used platelet aggregometry to assess aggregation induced by ristocetin, adenosine-5'diphosphate, arachidonic acid, epinephrine, and collagen. In this study, statistically significant defects in ristocetin-induced platelet aggregation were found to be more prevalent in black women with menorrhagia compared with black control women. (23)

The platelet function analyzer may be used as a screening test of abnormal platelet function. This test measures the time to plug formation (the closure time) when whole blood is introduced to membranes lined with epinephrine and collagen. (7) The utility of the platelet function analyzer as a tool for evaluating underlying bleeding disorders in women with menorrhagia is controversial. (26) The platelet function analyzer has good sensitivity to identify disorders of primary hemostasis, including PFDs and vWD, but has low specificity.

More detailed analysis of a suspected platelet disorder might include platelet electron microscopy and flow cytometry. Electron microscopy identifies platelet granules and cytoskeleton defects. Flow cytometry to analyze glycoprotein defects may confirm the presence of Bernard-Soulier syndrome and Glanzmann thrombasthenia by demonstrating decreased glycoprotein Ib and IIb/IIIa levels, respectively. (7)

Hemophilia Carrier States

Hemophilia A and B, deficiencies of FVIII and factor IX (FIX), respectively, are rare X-linked disorders characterized by the potential for spontaneous life-threatening bleeding and recurrent musculoskeletal hemorrhage leading to chronic arthropathy and disability. (27) The disorder typically affects men, and women are often categorized as being obligate carriers or possible carriers. Obligate carriers include all daughters of a father with hemophilia, mothers of 1 son with hemophilia and at least 1 other affected family member, or mothers of at least 2 affected sons. Possible carriers include daughters of a carrier, mothers of 1 son with hemophilia and no other family history, or female first- or second-degree relatives of a known carrier. (28) Factor levels may vary from one carrier to another; some carriers have levels low enough to exhibit a bleeding phenotype. This results from variable expression of the gene due to the random inactivation of 1 X chromosome seen in lyonization. The reference range of FVIII and FIX is 50 to 150 IU/dL. Bleeding manifestations typically occur when factor levels are less than 50 IU/dL. However, hemophilia carriers may manifest bleeding symptoms even with FVIII or FIX levels within the reference range. It is important that baseline levels are established so that appropriate anticipatory guidance or active management can be provided. Carriers with lower factor levels are at increased risk for severe bleeding episodes. (29)

Levels of FVIII are variable because they may increase transiently with stressful events and certain physiologic states, such as pregnancy, for which results interpretation should be conducted with caution. Certain FVIII gene mutations (intron 22 inversions, nonsense mutations, and large deletions) carry a high risk of inhibitor (antibody) formation. Inhibitors are antibodies (primarily immunoglobulin G) directed against the specific deficient factor; these antibodies bind to infused FVIII molecules, resulting in clearance from the circulation and continued bleeding. Gene sequence analysis may be indicated in cases in which FVIII replacement might need to be used.

The hallmark of hemophilic bleeding is hemarthrosis, but female carriers of hemophilia face the additional challenges of reproductive bleeding. Carriers are at increased risk for bleeding from hemorrhagic ovarian cysts. (29) Compared with women with normal clotting factor levels, women with factor levels less than 0.4 IU/mL more often reported menorrhagia and iron deficiency anemia. (29)

In the United States, males with hemophilia have access to insurance coverage and comprehensive health-care, including factor infusion. Females may not be eligible for insurance coverage if diagnosed as a symptomatic carrier. (28) This disparity has resulted in elimination of the diagnosis of symptomatic carrier in favor of mild hemophilia. Most female carriers maintain factor levels that qualify to classify them as having mild hemophilia. Mild hemophilia is defined as a FVIII or FIX level of 5 to 40 IU/dL. However, few females qualify as having moderate (FVIII or FIX levels of 1–5 IU/dL) or severe (FVIII or FIX levels <1 IU/dL) hemophilia, depending on the extent of lyonization. Changing International Classification of Diseases coding to mild hemophilia is sufficient to allow third-party payers to cover the medical care of the mild hemophilic female.

Factor XI Deficiency and Other Rare Bleeding Disorders

Rare bleeding disorders, including deficiency of fibrinogen (FI), FII, FV, FVII, FX, FXI, FXIII, as well as combined factor deficiencies, represent 3% to 5% of all inherited coagulation disorders. (28) Rare bleeding disorder are characterized by a variety of symptoms, ranging from mild to severe, which can vary significantly from one disorder to another and among patients with the same disorder. The bleeding phenotype is often expressed in patients who are homozygous or compound heterozygous. The correlation between the factor level and the bleeding tendency can also vary markedly between deficiencies and between patients affected by the same deficiency. Factor XI deficiency is increasingly recognized as a cause of reproductive bleeding. Factor XI deficiency, also called hemophilia C, or Rosenthal syndrome, was first recognized in 1953 in patients who experienced severe bleeding after dental extractions. The incidence is 1 in 100,000 persons in the general population. (30) It is increased among persons of Ashkenazi Jewish descent. It is an autosomal recessive disorder. In plasma, FXI circulates in association with high-molecular-weight kininogens and plays an important role in contact activation of the coagulation cascade. A deficiency of FXI may manifest as injury-related bleeding but has also been associated with epistaxis and easy bruising. (30) A review published by Wiewel-Verschueren et al (31) revealed that women with inherited FXI deficiency were at increased risk for HMB and bleeding complications after miscarriage, termination of pregnancy, and delivery. Heavy menstrual bleeding was reported in 7% to 67% of women observed. (31) Studies related exclusively to adolescents are limited.

Additional laboratory evaluation of all adolescent females with a suspected bleeding disorder should include a pregnancy test, tests of thyroid function (thyrotropin and free thyroxine levels), a prolactin level, a dehydroepiandrosterone-sulfate level, and a total testosterone level. Irregular bleeding can occur with dysthyroid states, hyperprolactinemia, and polycystic ovarian syndrome.

Referral to a hematologist is recommended if there is suspicion of a bleeding disorder from history, physical examination, or laboratory test findings. Figure 3 provides an algorithm for the diagnostic evaluation of the adolescent with menorrhagia and a suspected bleeding disorder.

MANAGEMENT STRATEGIES FOR THE ADOLESCENT WITH MENORRHAGIA AND AN INHERITED BLEEDING DISORDER

A multidisciplinary approach to patient management involving hematologists, obstetrician/gynecologists, and adolescent medicine specialists is appropriate. Bleeding is best managed in the context of the acuity and severity of blood loss. Life-threatening blood loss and severe anemia warrant hospital admission, intravascular fluid repletion, blood product transfusions, and replacement of clotting factor concentrates when indicated. Long-term goals should include reducing the morbidity associated with HMB and improving the patient's health-related quality of life. Therapy should aim to regularize the menstrual cycle or halt bleeding entirely, correct anemia, and limit the occurrence of problematic bleeding episodes. (32) In older patients, endometrial ablation or hysterectomy may become options, but for women in their reproductive years, where the need to preserve fertility is a priority, medical management forms the mainstay of therapy. Available treatment options include those recommended for women and girls without bleeding disorders but with heavy menstrual flow. Hormonal and hemostatic treatment options are available. Generally, hormonal treatments are used first, with the addition of hemostatic agents as necessary to control bleeding. For women with an identified bleeding disorder, treatment may be more patient-specific. For example, documentation of an appropriate response to desmopressin allows for this medication to be used in vWD or hemophilia A. A combination of therapies is often required. To date there have been no large randomized trials to specifically address treatment of HMB secondary to bleeding disorders in the adolescent population. A general approach to treatment is provided in Fig 4. Explaining the benefits and potential adverse effects of treatment is essential to optimize adherence to a prescribed regimen.

Hormonal Methods of Management

Hormonal modalities include COCPs, levonorgestrel-releasing intrauterine systems (LNG-IUS), oral progestins, injected progestogens, and short courses of gonadotrophin-releasing hormone (GnRH) analogues. These medications inhibit endometrial proliferation, which decreases the potential for extensive bleeding. The COCPs are most often

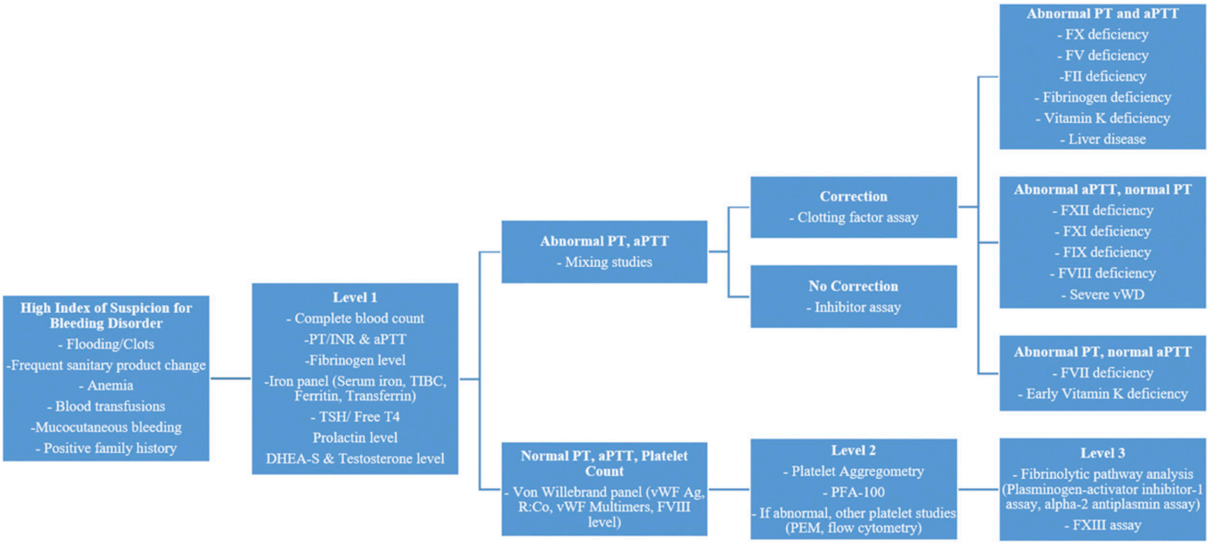


Figure 3. Diagnostic algorithm for the evaluation of the adolescent with menorrhagia. aPTT=activated partial thromboplastin time; FII/V/VII/VIII/IX/X/XI/XII/XIII=Factosr II/V/VII/VIII/IX/X/XI/XII/XIII; PEM=platelet electron microscopy; PFA=platelet function analyzer; R:Co: ristocetin cofactor; TIBC=total iron binding capacity; TSH=thyroid stimulating hormone; T4=thyroxine; vWF Ag=von Willebrand factor antigen; vWD=von Willebrand disease.

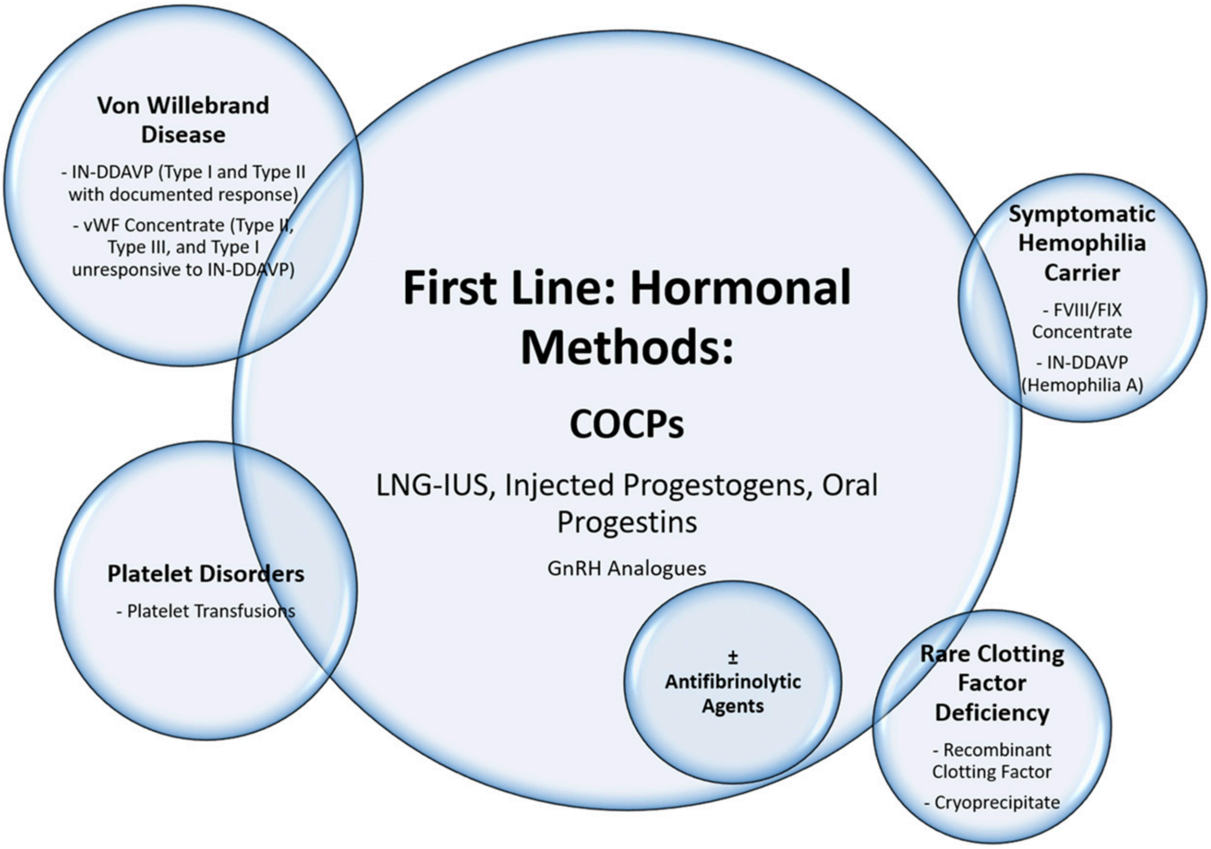

Von Willebrand Disease
- IN-DDAVP (Type I and Type II with documented response)
- vWF Concentrate (Type II, Type III, and Type I unresponsive to IN-DDAVP)
First Line: Hormonal Methods:
COCPs
LNG-IUS, Injected Progestogens, Oral Progestins
GnRH Analogues
Symptomatic Hemophilia Carrier
- FVIII/FIX Concentrate
- IN-DDAVP (Hemophilia A)
Platelet Disorders
- Platelet Transfusions
± Antifibrinolytic Agents
Rare Clotting Factor Deficiency
- Recombinant Clotting Factor
- Cryoprecipitate

Figure 4. Approach to the management of menorrhagia in the adolescent.
COCP=combined oral contraceptive pill; GnRH=gonadotropin-releasing hormone; IN-DDAVP=intranasal 1-deamino-8-D-arginine vasopressin; FVIII/FIX=factors VIII/IX; LNG-IUS=levonorgestrel-releasing intrauterine system; vWF=von Willebrand factor.

the method of choice for adolescents and have been shown to reduce menstrual loss, correct iron deficiency anemia, and improve quality of life. (24)(32) Multiple formulations are available with varying estrogen concentrations, which allows for augmentation of treatment if initial low doses fail to control HMB. Therapy is often initiated at high doses in the immediate period after achieving hemodynamic stability to gain control of or to prevent hemorrhage. In the long-term, COCPs are useful for cycle regulation and improvements in dysmenorrhea and premenstrual tension. (32) Use of COCP has the added advantage of suppressing ovulation bleeding. Extended or continuous cycles of COCPs for 3 months or more can induce temporary amenorrhea in adolescents and reduce the frequency and severity of menstrual bleeding. (32) This regimen allows control of the timing of bleeding. In a retrospective review by Chi et al, (33) one-third of girls on this regimen experienced breakthrough bleeding, which was generally light and well tolerated. A potential complication of COCP use is an increased risk of thrombosis. The risk is very low in adolescent girls in general, especially in those with a bleeding diathesis. (32) Smoking, malignancy, and autoimmune conditions increase the hypercoagulability risk. Screening for these risk factors should be a part of the initial history. A personal or family history suggestive of thrombophilia, particularly in first-degree relatives, may be a contraindication to COCP use. Other common adverse effects of COCPs include headache, bloating, breast tenderness, weight gain, and nausea and vomiting. (32) The severity of these symptoms tends to decline with use over time. In a study by Amesse et al, (22) the use of COCPs in adolescents with vWD type 1 was evaluated and it was found that COCPs alleviated menstrual blood loss in 86% of patients, as determined by the PBAC score.

An LNG-IUS is a hormonal reservoir inserted into the uterus. Similar to the COCP, the LNG-IUS reduces menstrual bleeding by limiting proliferation of the endometrium, but with a steady intrauterine delivery of levonorgestrel at a rate of 20 μg/24 hours. An LNG-IUS is effective in managing menorrhagia in women with bleeding disorders. The hypercoagulable potential is minimal. Chi et al (33) studied the effects of an LNG-IUS on women with bleeding disorders, including

13 women with vWD, all of whom reported a significant improvement in their quality of life and a decrease in blood flow. Previously, the lack of evidence of safety in adolescents, possible increased risk of device expulsion, and hesitancy to use in the virginal female account for less frequent use of this method. (33) The 2011 ACOG Clinical Management Guidelines confirmed the safety of intrauterine devices for women, including adolescent girls. There have been no studies demonstrating an increased risk of pelvic inflammatory disease with LNG-IUS use in the nulliparous female, and there is no evidence that its use is associated with subsequent infertility. (34) Oral progestins, injected progestogens, and GnRH analogues have been less studied in adolescents, but there have been reports of their use in the literature. (33) Oral progestins have a particular role in the management of patients with inherited or acquired thrombophilic disorders, who have an increased risk of thrombosis with estrogen-containing agents. Analogues of GnRH are very effective in controlling menorrhagia; but because of the potential adverse effects of hypoestrogenemia and subsequent osteopenia they are generally not prescribed for young adolescent girls. The GnRH analogues with add-back therapy can be considered as a final medical option for girls with severe bleeding not controlled by other measures. (33)

Hemostatic Therapy

Hemostatic agents demonstrated to be effective in controlling menorrhagia in women with bleeding diatheses include desmopressin, antifibrinolytic medications (tranexamic acid [TA] and aminocaproic acid), and clotting factor concentrates. These methods may be used alone but are more often used in combination or in addition to the hormonal methods already described.

Desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]), a synthetic analogue of antidiuretic hormone, releases endothelial stores and increases plasma vWF and FVIII levels transiently in healthy individuals, in individuals with vWD, and in persons with mild hemophilia A. (12)(29)(35) It is most effective in patients with type 1 vWD, who have normal vWF available for release from storage sites, and is ineffective in patients with type 3 disease. Response is variable in type 2 vWD, depending on the dysfunction. It may also be used in some mild PFDs. It is important to document patient response to a DDAVP challenge before prescribing this medication. The DDAVP can be administered intravenously or subcutaneously at a dose of 0.3 μg/kg or as an intranasal spray by a metered-dose inhaler at a fixed dose of 150 or 300 μg. (10)(32)(35) The intranasal spray is convenient for outpatient, in-home use. The use of DDAVP for menorrhagia associated with vWD has been extensively studied in adults, but experience is limited in adolescent girls. Studies to evaluate the effectiveness of intranasal DDAVP in controlling HMB in adolescents with bleeding disorders, including vWD, platelet dysfunction, and symptomatic mild hemophilia A, have demonstrated significant reduction in bleeding assessment scores from baseline. (12)(36)(37)

A limitation of DDAVP use is tachyphylaxis, secondary to depletion of available endothelial stores of vWF, (35) which typically occurs after 2 or 3 days of consecutive use. These stores replenish after 10 to 14 days. It is generally recommended not to take more than 2 doses in a 2-week period. Other adverse effects include facial flushing, headaches, and nausea. (6)(32)(35) Perhaps the most critical albeit infrequent complication is the risk of dilutional hyponatremia, secondary to water retention, which may lead to seizures. (35) It is important to counsel patients against using DDAVP more frequently than 2 administrations daily at 12-hour intervals (15) and to limit excessive free water intake during periods of use.

Higher levels of fibrinolysis occur in the endometrium and menstrual fluid of women with HMB than in controls. (6) Antifibrinolytic therapy can be used alone or in addition to other therapies for the prevention and management of menorrhagia. There have been no large systematic trials demonstrating the efficacy of these agents in adolescents with an underlying bleeding disorder. However, beneficial effects on quality of life and bleeding assessment scores have been documented. Aminocaproic acid is a strong competitive inhibitor of both plasminogen activator and plasmin itself. It may be administered orally or intravenously to control menorrhagia. Tranexamic acid, a synthetic lysine derivative, adheres to the lysine receptor binding sites on plasmin, inhibiting attachment of fibrin monomers and slowing clot disintegration. (38) A prospective crossover study compared the ability of intranasal DDAVP and TA to reduce menstrual blood loss. The study demonstrated a statistically significant decrease in PBAC scores for both treatments, although the decrease in PBAC score was greater for TA than for intranasal DDAVP. (39) A similar study of oral TA versus COCPs demonstrated significant improvement by both TA and COCPs in menstrual blood loss, but no significant difference was noted between the 2 interventions. (40)

Antifibrinolytic medications are generally well tolerated. Nausea, emesis, and diarrhea have been the most frequently reported adverse effects. (38)(40) Prolonged use of TA has rarely been associated with changes in color vision. (29)

Most managed patients have improved long-term outcomes. A small percentage of women with vWD will require the use of vWF replacement because of failure to respond to

DDAVP, or when DDAVP is contraindicated, such as patients who have either severe type 1 vWD or type 2 or 3 vWD. In these patients with intractable menorrhagia, virally inactivated plasma-derived vWF concentrates can be administered. These concentrates often contain varying amounts of FVIII. The typical dose is 20 to 40 U/kg of vWF ristocetin cofactor unit for menorrhagia. (12)(41) A recombinant vWF concentrate has recently become commercially available. Use of this product eliminates the risk of accumulating potentially thrombogenic FVIII. (12) Although recombinant factor concentrates are available for FVII, FVIII, FIX, and FXIII, the use of these agents to exclusively control HMB in the adolescent has not been systemically studied.

CONCLUSION

Menorrhagia secondary to underlying bleeding disorders is common among adolescent females. Bleeding disorders in adolescents and young women, when unrecognized, pose challenges for patients and their families and also carry significant public health implications. There remains a need for consideration by clinicians of a possible diagnosis of a bleeding disorder in patients with HMB. Comprehensive evaluation and management is best accomplished with a multidisciplinary team involving a hematologist, a gynecologist, an adolescent medicine specialist, and a primary care physician. Controlling menorrhagia in these adolescent girls often requires a combination of treatment modalities. The mainstay of managing menorrhagia is hormonal therapy, with the addition of hemostatic agents as needed. Management should aim to reduce the frequency and severity of bleeding episodes and increase health-related quality of life. Well-designed clinical trials focused on the adolescent patient to provide high-quality evidence for optimal diagnostic and therapeutic approaches are essential.

Summary

- On the basis of epidemiologic studies and expert opinion, the adolescent female presenting with menorrhagia should be evaluated for a bleeding disorder. (8)(13)
- On the basis of expert opinion and consensus guidelines, menorrhagia is defined as menstrual bleeding lasting for more than 7 days, sanitary product use greater than 7 per day, and a greater than 80-mL blood loss per menstrual cycle. (1)
- On the basis of observational studies and expert opinion, a history of flooding and/or impairment of daily activities with periods, soaking through night clothes, passing clots greater than 1 inch in diameter, and iron deficiency anemia often identify patients with menorrhagia. (14)
- On the basis of observational studies, the pictorial bleeding assessment calendar and the bleeding assessment questionnaire can be used to objectively quantify menstrual losses. (15)(42)
- A thorough diagnostic evaluation includes studies for von Willebrand disease, platelet function defects, hemophilia A and B, and rarer clotting factor deficiencies. On the basis of observational studies, it is now appreciated that female carriers of factor deficiency often have symptomatic menorrhagia, even when factor levels are normal. (29) African American females investigated for menorrhagia more often have platelet function disorders than do white females. (23)
- On the basis of observational studies and expert opinion, hormonal and hematologic treatment options are effective in controlling HMB in adolescents. (22)(24)(12)(33)(32)(40)(39) A combination of treatment modalities is often required to control menorrhagia.
- On the basis of expert opinion, comprehensive management is best achieved when it involves a hematologist/oncologist, an obstetrician/gynecologist, and a primary care physician.

References for this article are at http://pedsinreview.aappublications.org/content/39/12/588.

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1. An almost 13-year-old girl presents to the clinic with a 6-month history of heavy menstrual bleeding. The patient had her first menstrual period 8 months ago. Her periods have been occurring irregularly at approximately 18- to 28-day intervals, each lasting 7 to 10 days with heavy flow soaking approximately 7 pads per day during each period. Her last menstrual period was 2 weeks ago. There is no history of gum bleeds or easy bruising. She takes no medications except for a total of 3 doses in the past 6 months of nonsteroidal anti-inflammatory drugs for menstrual pain. She is not taking oral contraceptive pills and is not sexually active. On physical examination she appears to have Tanner 3 breasts and slightly pale conjunctivae. Her parents are worried about the cause of the heavy bleeding. Which of the following is the most appropriate next step in the management of this patient?
   - A. Discontinue nonsteroidal anti-inflammatory drug use.
   - B. Order a coagulation evaluation.
   - C. Pelvic ultrasonography.
   - D. Reassurance and watchful waiting.
   - E. Start oral contraceptive pills and follow up in 1 to 2 months.
2. For the patient in question 1, laboratory studies were obtained and results are pending. On family history, her father reports a history of epistaxis. Her mother describes her own menses as being normal. Which of the following is the most likely underlying potential hematologic cause of menorrhagia in this patient?
   - A. Hemophilia A.
   - B. Hemophilia B.
   - C. Immune thrombocytopenic purpura.
   - D. Inherited platelet function defect.
   - E. Von Willebrand disease.
3. A 12-year-old girl develops menorrhagia with her first 4 menstrual cycles. There is no history of abdominal pain, fevers, vomiting, or vaginal discharge. She has a history of epistaxis several times in the past. The patient is seen in the clinic, and laboratory studies are ordered. Which of the following laboratory tests is most likely to identify the underlying cause of her heavy menstrual bleeding?
   - A. Bleeding time.
   - B. Complete blood cell count.
   - C. Partial thromboplastin time.
   - D. Platelet function studies.
   - E. Von Willebrand factor assays.
4. A 15-year-old African American girl has had menorrhagia since menarche at 13 years of age. Complete blood cell count showed a hemoglobin level of 9 g/dL (90 g/L) and a mean corpuscular volume of 65 μm^3 (65 fL) with normal white blood cell and platelet counts. She was started on oral iron therapy, which resulted in increasing her hemoglobin level to 11.3 g/dL (113 g/L) 3 weeks later. Von Willebrand factor assay results were all above the mean. Which of the following is the most appropriate follow-up study to investigate the possible cause of her menorrhagia?
   - A. Factor IX levels.
   - B. Flow cytometry examining glycoprotein defects.
   - C. Platelet aggregometry.
   - D. Platelet electron microscopy.
   - E. Platelet function analyzer.

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5. A 16-year-old girl reports heavy menstrual bleeding. Her menses usually last 7 or 8 days and often require 8 or 9 sanitary products per day on the day of heaviest flow. A diagnostic evaluation revealed the diagnosis of platelet function defect. She has a mild microcytic anemia, which responds to oral administration of ferrous sulfate. Which of the following is the most appropriate initial therapy to reduce blood loss in this patient?
    A. Combined oral contraceptive pills.
    B. Desmopressin.
    C. Gonadotrophin-releasing hormone analogues.
    D. Levonorgestrel-releasing intrauterine system.
    E. Monthly platelet transfusions.

Aplastic and Hypoplastic Anemias

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Education Gaps

1. Anemia is a common finding in general pediatrics, but knowing when to refer a patient can be challenging.
2. Pediatricians do not always order reticulocyte counts as part of the evaluation of anemia. The reticulocyte count, interpreted in the context of the mean corpuscular volume, is very useful in the development of differential diagnoses for anemia and determination of urgency of referral.
3. Pediatricians (and subspecialists) may not realize that diagnosis of malignancy, particularly head and neck cancers, at an unexpectedly early age may be associated with an inherited bone marrow failure.

Objectives After completing this article, readers should be able to:

1. Assess the need for referring a patient with anemia based on whether anemia is isolated or accompanied by other hematologic or physical anomalies.
2. Recognize that anemia in the setting of congenital anomalies may signify an inherited bone marrow failure disorder.
3. Understand that inherited bone marrow failure disorders confer a higher risk of malignancy.

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ABBREVIATIONS

AA	aplastic anemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ARC	absolute reticulocyte count
CBC	complete blood cell
DBA	Diamond-Blackfan anemia
DC	dyskeratosis congenita
FA	Fanconi anemia
GPI	glycosylphosphatidylinositol
HSCT	hematopoietic stem cell transplant
MCV	mean corpuscular volume
MSD	matched sibling donor
MUD	matched unrelated donor
OS	overall survival
PNH	paroxysmal nocturnal hemoglobinuria
PRCA	pure red cell aplasia
SDS	Shwachman-Diamond syndrome
TEC	transient erythroblastopenia of childhood

INTRODUCTION

Children with anemias often initially present to their pediatricians. Anemia may result from blood loss, a destructive process (ie, hemolysis), nutritional deficiency, or poor production (eg, ineffective erythropoiesis or hypoplastic or aplastic marrow) (Table). Hemolytic and nutritional anemias have been discussed elsewhere and are referenced briefly in this article. (1)(2)(3)(4) This review focuses on the broad differential diagnosis for anemia associated with poor production. These anemias can lead to chronic morbidity and require subspecialty care, whereas others may be managed effectively in primary care. This review offers a framework to guide evaluation and the need for subspecialty investigation.

TABLE. Classification of Anemias by Mechanism and Notable Associated Laboratory Data

MECHANISM OF ANEMIA	EXAMPLES	CHANGES IN LABORATORY DATA
Loss or destruction	Bleeding	↑ Reticulocyte count
	Autoimmune hemolytic anemia Hereditary spherocytosis Sickle cell anemia	↑ Reticulocyte count ↑ LDH ↑ Indirect bilirubin ↓ Haptoglobin
Nutritional deficiency	Iron deficiency	↓ MCV ↓ Reticulocyte count ↓ Ferritin ↓ Iron saturation ↑ TIBC
	Folate deficiency Vitamin B_{12} deficiency	↑ MCV ↓ Reticulocyte count
Poor production	Anemia of chronic inflammation	Normal or ↓ MCV ↓ Reticulocyte count
	Pure red cell aplasia	↑ MCV ↓ Reticulocyte count
	Aplastic anemia	↑ MCV ↓ Reticulocyte count +/– Neutropenia +/– Thrombocytopenia

LDH=lactate dehydrogenase; MCV=mean corpuscular volume; TIBC=total iron binding capacity.

PATHOGENESIS

Aplastic and hypoplastic anemias are characterized by impaired erythropoiesis due to decreased hematopoietic cells in the bone marrow. Impairment of erythropoiesis can result from an acquired condition or an inherited defect in marrow function. Acquired conditions may include parvovirus infection of erythrocyte precursors or T-cell–mediated destruction of hematopoietic cells in acquired aplastic anemia. Inherited defects in marrow function can present at any point throughout the life span with progressive anemia.

Impaired erythropoiesis can also result from abnormal metabolism of iron, which is a critical component of hemoglobin. Although this class of disorders is not associated with marrow hypoplasia, it should still be considered as part of the differential diagnosis for anemia with reticulocytopenia (Fig).

CLINICAL FINDINGS

A thorough history and physical examination will provide important clues to the presence and potential causes of anemia. Patients with anemia may be asymptomatic or may present with pallor or fatigue. Infants and children with anemia may display irritability, poor feeding, or growth failure. A detailed dietary history may reveal a nutritional deficiency. Fever or symptoms of a viral illness preceding new-onset anemia could imply an infectious etiology. Anemia of chronic disease may be accompanied by symptoms related to the underlying condition. Inherited causes of anemia can be associated with short stature, skeletal abnormalities, or other congenital anomalies. Early-onset head and neck tumors can be the first presentation of Fanconi anemia. (5) The most common inherited bone marrow failure syndromes are considered cancer predisposition syndromes.

LABORATORY FINDINGS

The most helpful initial tests for the evaluation of any form of anemia include the complete blood cell (CBC) count, differential count, and reticulocyte count with indices. A normal or decreased reticulocyte count in the setting of anemia generally represents an inappropriate compensatory response and may be an indication of impaired erythropoiesis or marrow hypoplasia. An elevated reticulocyte count reflects a response to blood loss or hemolytic anemia. Mean corpuscular volume (MCV), reported as part of the CBC count, can guide the clinician in developing a differential diagnosis. In children older than 1 year, MCV less than 80 μm^3 (<80 fL) is considered microcytic, and 80 to 100 μm^3 (80–100 fL) is normocytic. Macrocytosis is defined as MCV greater than 100 μm^3 (>100 fL). Microcytosis could reflect iron deficiency, whereas macrocytosis may be concerning for vitamin B_{12}

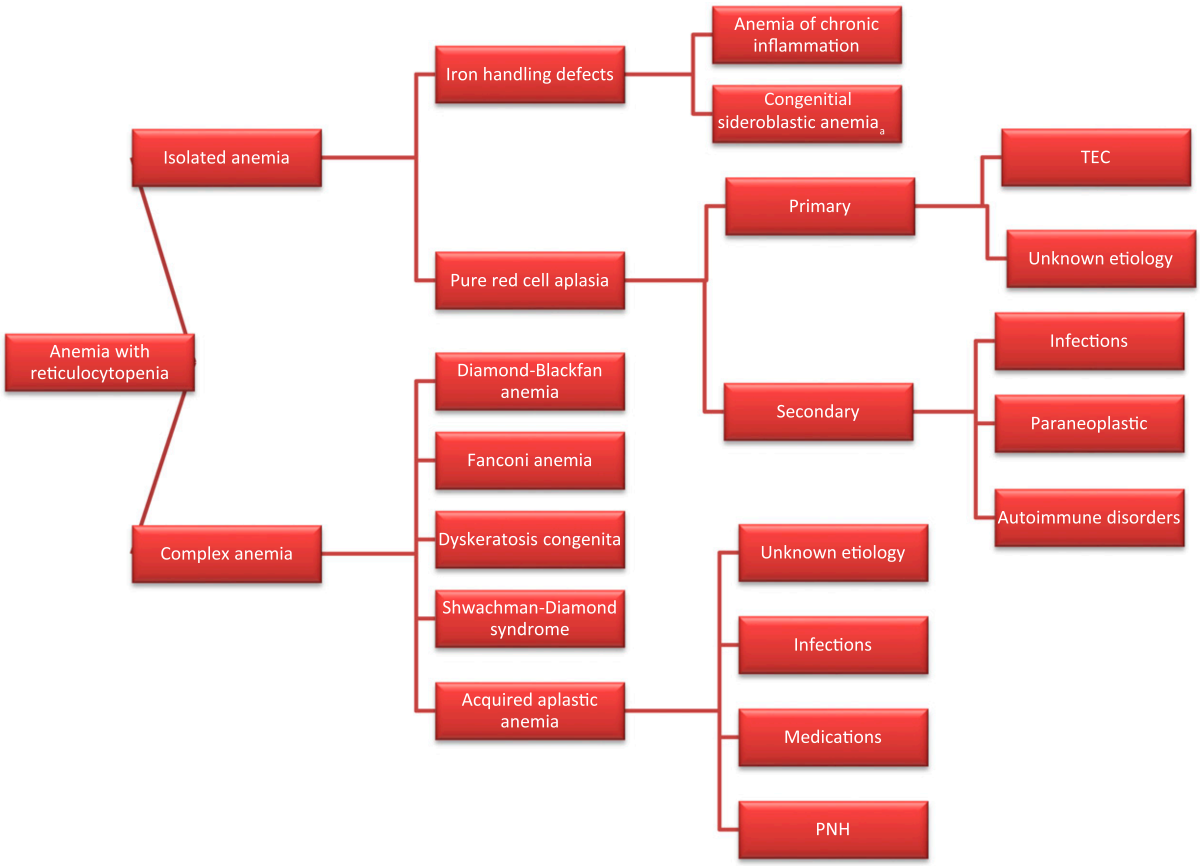

Figure. Classification of anemia with reticulocytopenia based on association with additional hematologic or physical anomalies.[a] There are rare syndromic forms of sideroblastic anemia associated with physical anomalies.
TEC=transient erythroblastopenia of childhood.

or folate deficiency or marrow failure. Concomitant neutropenia and/or thrombocytopenia are worrisome for more severe pathology, such as aplastic anemia or leukemia.

Additional blood work may be ordered based on clues from the initial evaluation. A peripheral blood smear may reveal microcytosis and hypochromia in an iron-deficient patient. Iron deficiency may also be accompanied by low ferritin level, increased iron-binding capacity, and low transferrin saturation. Ferritin, an acute phase reactant, can be within the reference range if iron deficiency and inflammation are both present. Vitamin B_{12} and folate levels should be measured if macrocytosis is observed. Hemoglobin electrophoresis provides an analysis of the types of hemoglobin expressed by an individual. Increased fetal hemoglobin level, in conjunction with progressive macrocytosis, may be signs of stress erythropoiesis and can be a harbinger of acquired or inherited bone marrow failure. (6)(7)

ANEMIA IN GENERAL PEDIATRICS

When confronted with newly discovered anemia with reticulocytopenia, the general pediatrician should consider the clinical context in conjunction with the blood work to determine the need for referral. In a well child without organomegaly or significant lymphadenopathy, it may be reasonable to monitor isolated normocytic anemia until the hemoglobin level normalizes. The frequency of monitoring depends on the severity of anemia. Surveillance blood work every 1 to 4 weeks may be sufficient for mild to moderate anemia. The development of severe anemia possibly requiring transfusion, constitutional symptoms (eg, fatigue, weight loss, night sweats, unexplained fevers, increased bleeding, or bruising), or other cytopenias represents a complex clinical picture and should prompt urgent referral to the pediatric hematologist/oncologist. Persistent macrocytosis or anemia in a child with congenital anomalies may raise concern for an inherited bone marrow failure syndrome and requires evaluation and close monitoring by pediatric hematology/oncology.

Classification of aplastic and hypoplastic anemias based on clinical complexity may be of practical utility for clinicians. For the purposes of this review, clinical complexity is defined by whether the anemia is isolated or associated with physical or other hematologic anomalies (Fig).

ISOLATED ANEMIAS

Usually microcytic or normocytic, anemia due to chronic inflammation is extremely common and is the end product of several processes. Inflammation increases expression of hepcidin, a key regulator of iron metabolism, and interleukin-6, a proinflammatory cytokine. (8) Through its effect on ferroportin, hepcidin activity leads to decreased gastrointestinal iron absorption and increased iron sequestration in macrophages, reducing its availability for erythropoiesis. (9) Interleukin-6 promotes iron sequestration by upregulation of hepcidin via the *JAK/Stat* pathway. (10) Other proinflammatory cytokines, such as interleukin-1, tumor necrosis factor α, and interferon-γ, seem to inhibit erythropoiesis by impairing erythropoietin sensitivity and erythroid lineage differentiation. (11)(12) Currently, the most effective intervention for anemia of chronic inflammation is to treat the underlying disease, but experimental treatments are being studied. (8)

Congenital sideroblastic anemias comprise a group of uncommon inherited anemias defined by ringed sideroblasts in the bone marrow. This morphologic finding represents iron deposition in the mitochondria of erythroid precursors, a result of impaired mitochondrial iron handling and abnormal heme synthesis. Sideroblastic anemias may be microcytic, normocytic, or macrocytic. A variety of mutations have been implicated, but the most commonly affected gene is *ALAS2*, which encodes a critical enzyme involved in the production of heme. *ALAS2* deficiency is X-linked but can also affect girls and women due to lyonization. Patients with congenital sideroblastic anemia can have mild to severe forms of anemia with concomitant iron overload, even in the absence of transfusion dependence. Anemia with elevated ferritin and transferrin saturation should prompt referral to a pediatric hematologist to further investigate whether this disorder may be present. Pyridoxine (vitamin B_6) has historically been used to treat anemia. Iron overload may be addressed by chelation therapy or phlebotomy. (13)(14)

Acquired pure red cell aplasia (PRCA) encompasses a heterogeneous set of disorders causing normocytic, normochromic anemia and a selective decrease in erythroid progenitors. Pure red cell aplasia has been associated with infections, medications, (15)(16) malignancies, and underlying autoimmune disorders. (17) When an etiology cannot be identified, it is designated as primary PRCA. Most cases of primary and secondary PRCA are thought to be immune mediated. This is supported by reports of association with autoimmune diseases, such as rheumatoid arthritis and lupus. Pure red cell aplasia can also be paraneoplastic, preceding or in association with several malignant processes, such as thymoma, (18) Hodgkin (19) and non-Hodgkin lymphoma, (20) and large granular leukemia. (21) Immunoglobulin G and T- and natural killer–cell–mediated PRCA have been described. (22) The incidence of PRCA after ABO-mismatched allogeneic hematopoietic stem cell transplant (HSCT) was 7.5% in one case series. (23)

Pure red cell aplasia may be suspected in patients with persistent normocytic, normochromic anemia and reticulocytopenia. The absolute reticulocyte count (ARC) is uniformly less than $10\times10^3/\mu L$ ($10\times10^9/L$). If clinically warranted, secondary causes of PRCA should be ruled out. A bone marrow examination is necessary for diagnosis. Aside from decreased or absent erythroid progenitors, the bone marrow should be normal, without dysplasia or cytogenetic abnormalities. (17)

Primary PRCA is treated with immunosuppression, with cyclosporine with or without corticosteroids achieving the most durable responses. (17) Treatment of secondary PRCA is usually directed at the underlying etiology.

Parvovirus B19 infection is a classic cause of PRCA. A marker of past infection, parvovirus immunoglobulin G is present in 2% to 15% of children aged 1 to 5 years and 15% to 60% of children aged 6 to 19 years. (24) The virus preferentially infects red blood cell precursors by binding to the blood group P antigen on these cells. (25) Individuals who do not express P antigen are resistant to parvovirus infection. The resulting death of erythroid progenitors temporarily halts erythropoiesis, causing a transient anemia. Immunocompetent patients whose circulating red blood cells live long enough until the viral infection is cleared generally experience no sequelae. In contrast, patients with a chronic hemolytic process such as sickle cell disease, in which erythrocyte life span is abbreviated, can develop life-threatening anemia. Immunocompromised patients may develop chronic parvovirus infection, most often manifesting as PRCA. Bone marrow examination may reveal unusually large pronormoblasts, which are the earliest red blood cell precursor. Polymerase chain reaction may be used to detect parvovirus DNA, although there is a risk of both false-positive and false-negative results. Pure red cell aplasia due to chronic parvovirus infection can be treated with intravenous immunoglobulin for several days. (26)

New-onset isolated normocytic anemia with reticulocytopenia in a healthy toddler may raise suspicion of transient erythroblastopenia of childhood (TEC), a type of PRCA. From 1987 to 1989, the incidence of TEC in Sweden was estimated to be 4.3 per 100,000 children younger than 3 years. (27) This is likely an underestimate because cases of mild to moderate anemia may have resolved untreated and were not reported. TEC has been reported less frequently in recent years. (28) An infectious etiology has been suggested, but no consistent pathogens have been identified. (29)(30)(31)

TEC primarily affects children aged 1 to 4 years, although infants can be affected. The anemia is often found incidentally in the setting of an illness or as part of an investigation of pallor in an otherwise vigorous child. A history of nonspecific viral symptoms may or may not precede the onset of anemia. The presenting hemoglobin level may sometimes be low enough to affect hemodynamic stability and thus warrant transfusion, but TEC is ultimately defined by spontaneous recovery starting within an average of 2 weeks after diagnosis. The recovery phase will be characterized by reticulocytosis and elevated fetal hemoglobin level. The bone marrow is not necessary for diagnosis but would show markedly decreased red blood cell precursors. A bone marrow examination is needed only if recovery of erythropoiesis does not occur as expected after 3 to 4 weeks or there are red flags in the clinical presentation. (28)

COMPLEX ANEMIAS

Diamond-Blackfan Anemia

TEC sometimes must be differentiated from Diamond-Blackfan anemia (DBA), especially in young children and infants. A rare inherited red cell aplasia, DBA is diagnosed in approximately 30 patients per year in the United States. (32) This is consistent with reports from other countries, where the annual incidence rate ranges from 4 to 7 cases per million births. (33)(34)(35)(36) Most patients with classical DBA are diagnosed in infancy, when they present with an unexplained macrocytic anemia with reticulocytopenia. Additional cytopenias can be seen but should prompt a search for other bone marrow failure disorders. Persistence of the hematologic findings warrants referral to the pediatric hematologist. Almost 50% of patients exhibit congenital anomalies, such as abnormal thumbs, short stature, facial dysmorphism, genitourinary anomalies, or cardiac defects. (37) Further investigation, ideally performed before transfusion, would reveal elevated erythrocyte adenosine deaminase and fetal hemoglobin levels in 80% to 85% of patients. In contrast, 90% of patients with TEC express normal levels of erythrocyte adenosine deaminase. Adenosine deaminase is a critical ubiquitous enzyme catalyzing purine residue metabolism, but its role in DBA is unknown. (38) The bone marrow examination, which is mandatory for diagnosis, demonstrates decreased or absent erythroid progenitor cells but otherwise normal cellularity. Alternative causes of red cell aplasia, such as viral infection, malignancy, and other bone marrow failure conditions, should be ruled out. (39)(40)

Genetics of DBA. Manifestations of DBA arise from autosomal dominant mutations in ribosomal genes, which increase vulnerability to apoptosis in ways that continue to be elucidated. The first gene to be identified, *RPS19*, is mutated in 25% of patients. *RPS19* plus several other ribosomal genes (*RPS24, RPS17, RPL35A, RPL5, RPL11, RPS7, RPS10, RPS26,* and *RPL26*) account for 54% of patients with DBA. (41) Discovery of these mutations has led to the diagnosis of many "nonclassical" cases, even in adulthood. Thus, DBA represents a spectrum of disease that can encompass minimal anemia to transfusion dependence, isolated macrocytosis, only congenital anomalies, or no medical abnormalities at all. (40)

Management of DBA. To maintain appropriate growth and cognitive development, regular red blood cell transfusions are initiated in infancy to keep pretransfusion hemoglobin levels higher than 8 g/dL (80 g/L). Chronic transfusions are associated with alloimmunization and iron overload, so after 1 year of age, prednisone is used at a dose of 2 mg/kg per day for no longer than 4 weeks. Clinicians have used glucocorticoids in patients with DBA for more than 50 years, but the mechanism by which they improve erythropoiesis is still under investigation. In a mouse model of DBA, glucocorticoids inhibited apoptosis and delayed differentiation, leading to a greater pool of erythroid progenitors. (42) Clinically, 80% of children respond to corticosteroids within 4 weeks, defined as maintaining a hemoglobin level of at least 9 g/dL (90 g/L) without transfusion. The remainder do not respond or are unable to tolerate dose tapering. A second trial of prednisone can be attempted a year later because some children become steroid responsive. Once a response is seen, the dose should be tapered slowly to a target dose of 0.5 mg/kg per day or 1 mg/kg every other day. (40) Those taking long-term corticosteroids require periodic evaluations of growth, cataract formation, and bone health. Patients who fail a taper require resumption of chronic transfusions.

Patients receiving transfusions require management of iron overload with appropriate chelation and organ function evaluation. Matched sibling donor (MSD) allogeneic HSCT can be considered during childhood if the patient remains transfusion dependent. Five-year overall survival (OS) after MSD HSCT reached 87.5% in a small series from the Diamond Blackfan Anemia Registry of North America. (43) Donors must be screened carefully to ensure that they are not asymptomatic carriers of DBA.

Ominously, DBA is now considered a cancer predisposition syndrome, with a cumulative incidence of solid tumor or acute myeloid leukemia (AML) of 20% by 46 years of age. (44) Guidelines on cancer surveillance in this population are not available yet, but clinicians should be aware of patients' vulnerability and have a low threshold to consider malignancy evaluation in the appropriate clinical setting.

Fanconi Anemia

Although rare, affecting 0.1 to 0.5 per 100,000 live births, Fanconi anemia (FA) is the most common cause of inherited bone marrow failure syndrome and may present with macrocytic anemia and reticulocytopenia, often accompanied by other cytopenias. Mild to moderate cytopenias, first emerging between 5 and 10 years of age, are present in more than 70% of patients at diagnosis. (45)(46) Congenital anomalies, including radial or thumb abnormalities, genitourinary malformations, abnormal skin pigmentation, gastrointestinal anomalies, microphthalmia, short stature, cardiac defects, and developmental delay are present with variable severity in 90% of patients at diagnosis. (47) Furthermore, the VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula with esophageal atresia, renal and limb anomalies) and VACTERL with hydrocephalus syndromes are frequently associated with certain mutations in the FA pathway: *FANCI*, (48) *FANCB*, (49) and *FANCD1/BRCA2*. (50)

Genetics of FA. To date, 20 FA or FA-like genes have been identified through mutation analysis, including *BRCA1*. Fanconi anemia is transmitted in an autosomal recessive manner, except *FANCB* mutations, which are X-linked. The FA pathway encompasses critical proteins involved in DNA crosslinking repair and genomic stability. (51)(52)(53) Defects in the FA pathway significantly increase patients' vulnerability to ionizing radiation and chemotherapy. (5) Diagnostic assays for FA capitalize on this by using chemicals that induce DNA crosslinking. If left unrepaired due to mutations in an FA gene, DNA replication is impaired and chromosomal aberrations develop. Chromosomal breakage studies using mitomycin C or diepoxybutane are the gold standard method of diagnosis for FA. If mosaicism is suspected (ie, clinical suspicion is high but chromosome fragility test results are negative), skin fibroblasts should be collected for testing. Next-generation sequencing is commercially available to identify pathogenic mutations. (45) Full siblings of patients with FA, even if asymptomatic, should be tested as well.

Management of FA. Once the diagnosis is established, surveillance for progressive health problems is imperative. Bone marrow failure ultimately develops in 50% of patients by age 40 years. Remarkably, patients with *FANCD1/BRCA2* exhibit a cumulative incidence of malignancy of 97% by 7 years of age. The risk of developing AML or solid tumors (predominantly head, neck, and gynecologic cancers, but other solid tumors also occur) conferred by other FA mutations is 20% or 30%, respectively, by age 40 years. (54) Regular examinations to detect head and neck cancers should start at age 10 years, accompanied by counseling about smoking and alcohol avoidance and good dental hygiene. Annual screening for gynecologic epithelial cancers should begin by age 13 years, with examination of external genitalia. Full gynecologic examinations should begin when women become sexually active or by age 18 years if not sexually active. Vaccination against human papillomavirus should be strongly considered. (55)

Matched sibling donor HSCT before the onset of AML achieves the best hematologic outcomes, so careful monitoring of CBC count with differential count and annual bone marrow morphology, cellularity, and cytogenetic testing is recommended. (56) The development of moderate to severe cytopenias due to bone marrow failure or the acquisition of clonal abnormalities such as monosomy 7, −7q, +3q, complex karyotype, or *RUNX1* abnormalities confers poor prognosis. Such patients should proceed to HSCT if a suitable match is available. (45) The addition of fludarabine as part of reduced-intensity preparative regimens has improved survival in this population, which had historically experienced excess treatment toxicity due to irradiation and alkylating agents. In a retrospective, multicenter trial, patients undergoing MSD HSCT since 2000 achieved OS of 76% at 5 years and 64% in matched unrelated donor (MUD) HSCT. This is in contrast to 68% and 43%, respectively, for transplants performed before 2000. (57) Second malignancies pose a high risk after transplant, with recipients carrying a 4.4-fold higher risk of head and neck cancer compared with patients who did not undergo transplant. (58) A recent prospective, multicenter trial using radiation-free conditioning regimens for MUD HSCT reported an OS of 80% at 3 years. (59) It remains to be seen whether elimination of radiation from the preparative region will ameliorate the long-term risks of posttransplant malignancy.

Patients without appropriate HSCT donors who develop bone marrow failure may be treated with androgens. The mechanism of androgen effect on hematopoiesis remains unclear but perhaps relates to effects on regulation of stem cell cycling. (60) Danazol, oxymetholone, and oxandrolone can improve erythropoiesis, with smaller improvements seen in platelet or leukocyte counts. Virilization, liver adenomas, and elevated transaminase levels are common sequelae of androgens. Androgens do not delay onset of myelodysplasia or AML.

OTHER INHERITED BONE MARROW FAILURE DISORDERS

Dyskeratosis congenita (DC) is another rare bone marrow failure syndrome that can present with macrocytic anemia and other cytopenias. The classic triad of DC includes lacy, reticulated rash, leukoplakia, and dysplastic nails, but these features may not all be present at the same time. Patients with DC are at higher risk for pulmonary fibrosis, bone marrow failure, myelodysplasia, AML, and solid tumors. (56) It is caused by several mutations in genes regulating telomerase stability and function, such as *DKC1*, (61) *TERT*, (62) and *TERC*. (63) As with FA, patients with DC require regular monitoring of CBC counts and marrow function. Nonmyeloablative HSCT is indicated if myelodysplasia or severe bone marrow failure is detected. Androgens may be used as a bridge or in lieu of HSCT if no suitable donor can be found. A cancer predisposition syndrome, DC is associated with malignancy in 40% to 50% of patients by age 50 years. Head and neck cancers are the most common, followed by squamous cell carcinoma of the skin and anus. (64)

If anemia is accompanied by neutropenia, Shwachman-Diamond syndrome (SDS) should be considered. Associated with biallelic mutations in the *SBDS* gene, SDS more commonly presents with neutropenia and exocrine pancreatic insufficiency. However, SDS can present with a variety of clinical findings, including transfusion-dependent anemia with other cytopenias, isolated macrocytosis, failure to thrive, and/or skeletal anomalies. Bone marrow failure or myelodysplasia may develop, which may progress to AML. Hematopoietic stem cell transplant can be curative, but outcomes are better if performed before the development of AML. (65)

ACQUIRED APLASTIC ANEMIA

Most patients with marrow failure do not harbor any known inherited genetic lesions and are ultimately diagnosed as having acquired aplastic anemia (AA). Acquired AA is estimated to affect 2 to 3 per million people per year, according to European registries. Asian countries have reported higher incidence rates, ranging from 3.9 per million in Bangkok, Thailand, to 7.4 per million in China. The age distribution is bimodal, affecting young adults and the elderly most frequently. (66) An immune-mediated process, the etiology is understood to be multifactorial, attributed to medications, infections, or environmental exposures in genetically susceptible individuals. Nevertheless, the etiology is usually not evident at diagnosis.

Patients may present with symptoms due to cytopenias, including fatigue or pallor due to anemia, increased bruising or bleeding due to thrombocytopenia, or mucosal ulcers or infections due to neutropenia. If left untreated, severe AA is usually fatal.

Diagnosis of AA

Aplastic anemia should be considered in a patient with 2 or more persistent cytopenias, with early referral made to a pediatric hematologist. Anemia is usually normocytic or macrocytic, accompanied by reticulocytopenia. Thrombocytopenia and/or neutropenia are also seen. Bone marrow biopsy examination is mandatory and would show decreased cellularity of all lineages. There is some variability, but most centers define severe AA as an absolute neutrophil count (ANC) less than $500/\mu L$, ARC less than $20\times10^3/\mu L$ ($20\times10^9/L$), platelet count less than $20\times10^3/\mu L$ ($20\times10^9/L$), and bone marrow cellularity less than 25% for age. Criteria for very severe AA is the same except ANC less than $200/\mu L$. Moderate AA is typically defined by a hemoglobin level less than 10 g/dL (100 g/L), ANC less than $1500/\mu L$, platelet count less than $50\times10^3/\mu L$ ($50\times10^9/L$), ARC less than $40\times10^3/\mu L$ ($40\times10^9/L$), and bone marrow cellularity 25% to 50%. (67) Other causes of pancytopenia should be ruled out, including viral infections such as hepatitis, myelodysplasia, leukemia, FA, DC, SDS, and paroxysmal nocturnal hemoglobinuria. Human leukocyte antigen (HLA) typing should be undertaken for the patient and any full siblings as soon as the diagnosis of AA is made to facilitate timely HSCT if the sibling is a match.

Management of AA

Patients may become transfusion dependent before definitive therapy proves effective. Stringent criteria for transfusion are necessary to avoid alloimmunization and graft rejection if the patient proceeds to HSCT. Transfusions are administered to alleviate symptoms rather than to correct laboratory values. Directed donations of blood products from family members are contraindicated because they may precipitate alloimmunization against potential hematopoietic stem cell donors. Prolonged severe neutropenia increases the risk of opportunistic infections. The development of fever in this setting requires collection of blood cultures and institution of broad spectrum empirical antibiotics at a minimum.

If the patient has an HLA MSD, first-line therapy for severe AA would be allogeneic HSCT. Bone marrow is preferred over peripheral blood stem cells because it confers a lower risk of graft-versus-host disease. Overall survival 3 to 5 years after upfront MSD HSCT is excellent, reaching greater than 90% in several series. (68)(69)(70) Ten-year OS for patients in a large series from Japan was 89.7%. (71)

Immunosuppression with horse antithymocyte globulin (72) and cyclosporine is used in severe AA if HSCT is not an option or in patients with moderate AA who are transfusion dependent. After immunosuppression, OS ranges from 75% to 87%, but event-free survival is only 33%. (68)(73) Patients who have shortened leukocyte telomeres at diagnosis of AA are at higher risk for relapse after immunosuppressive therapy as well as for clonal evolution, (74) but it is not standard practice to check telomere length before starting treatment. Published guidelines recommend treatment for 4 months before starting to slowly taper cyclosporine if there is a response or pursuing second-line treatment in the absence of hematologic recovery. Most clinicians continue cyclosporine therapy for at least 6 months if not longer. If there is no response to immunosuppression, MUD HSCT can be pursued. (73)(75)(76) With improvements in conditioning and supportive care, outcomes after MUD HSCT are almost as good as those after MSD HSCT. (77)(78)(79)

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria (PNH) is an underlying cause of AA in children. A small Italian multicenter trial diagnosed only 2.5% of children with AA with concomitant PNH, (80) whereas a retrospective series of pediatric AA reported a 20% prevalence of PNH. (81) Accounting for less than 10% of patients with PNH, childhood PNH is a clonal hematopoietic disorder that can be primarily associated with AA or hemolysis. The latter is classified as classical PNH. Some patients may also exhibit subclinical disease that does not require treatment. Thrombosis occurs more commonly in patients with hemolytic anemia. Patients with classical PNH may also experience nonspecific symptoms, such as abdominal pain, esophageal spasm, or erectile dysfunction. These are sequelae of ongoing intravascular hemolysis ultimately causing nitric oxide deficiency and dysregulation of smooth muscle tone. Aplastic anemia is a more common presenting condition in children (58%–83%) than in adults (16%–23%), (81)(82)(83)(84) whereas hemoglobinuria is relatively rare in children.

Pathophysiology of PNH

Manifestations of PNH result from a global deficiency of glycosylphosphatidylinositol (GPI) anchor proteins due to an acquired mutation in the *PIGA* gene. The GPI-anchored proteins are an important class of proteins and include blood group antigens, adhesion molecules, and complement regulatory proteins. Most of the clinical manifestations of PNH are specifically due to loss of CD55 and CD59 on the red blood cell surface. (85) CD59 normally prevents lysis of host cells by inhibiting formation of the membrane attack complex. CD55 inhibits C3 convertase, which leads to reduction in the amount of C3 cleaved. The absence of these GPI-anchored molecules leads to uncontrolled complement-mediated lysis and intermittent hemoglobinuria. The link between AA and PNH remains unclear, but the favored hypothesis is that PNH clones have a survival advantage in the setting of T-cell–mediated destruction of hematopoietic stem cells. (85)

Diagnosis of PNH

All patients diagnosed as having AA and those with unexplained nonimmune hemolytic anemia, hemoglobinuria, or thrombosis with unexplained cytopenias or hemolysis should be evaluated for PNH. The gold standard method of diagnosis uses peripheral blood flow cytometry with fluorescent aerolysin, which binds to the glycan segment of GPI anchor proteins. Paroxysmal nocturnal hemoglobinuria is diagnosed if there is severe deficiency of GPI-anchored proteins in at least 2 cell lines.

Management of PNH

Patients with classical PNH may be treated with eculizumab, a humanized monoclonal antibody directed against C5, thereby blocking the terminal complement pathway. A favorable safety profile has been reported in pediatric patients, (86) but eculizumab does not address AA, which is the presenting symptom for most children. Furthermore, eculizumab is expensive, is needed indefinitely, and is associated with increased risk of *Neisseria* infection.

There are few data on comparative outcomes of immunosuppression versus HSCT for AA associated with PNH, particularly in pediatrics, so the management approach is similar to that of acquired AA. Allogeneic HSCT can also be considered for recurrent severe thromboembolic disease or transfusion-dependent hemolytic anemia despite treatment with eculizumab.

ACKNOWLEDGMENTS

The author would like to thank Drs Craig Mullen and Gary Noronha for reviewing this manuscript.

Summary

- Based on some research evidence as well as consensus, (28)(37)(39)(45)(65)(67)(81) a broad differential diagnosis exists for hypoplastic anemias but can be developed rationally by accounting for concomitant congenital anomalies, mean corpuscular volume, reticulocyte count, and other affected hematopoietic cell lines.
- Based primarily on consensus due to lack of studies examining this question, the severity of anemia or the complexity of the clinical context can help clinicians decide on the need for referral.
- Based on strong research evidence, (16)(17)(20)(23)(26)(27)(32)(51)(66)(84) hypoplastic or aplastic anemias may be acquired or congenital.
- Based on strong research evidence, (5)(44)(54)(64) the inherited bone marrow failure syndromes are also cancer predisposition syndromes. Early presentation of malignancy may suggest an underlying bone marrow failure syndrome.

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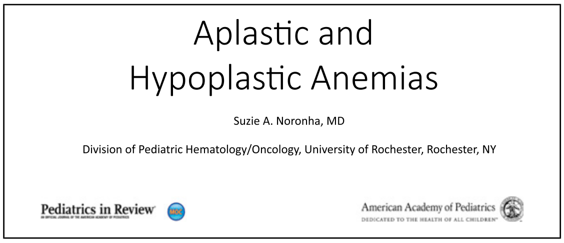

Aplastic and
Hypoplastic Anemias

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1. A 2-year-old girl is brought to the clinic because of pallor after a febrile illness 2 weeks ago. Her vital signs and physical examination findings are normal. The complete blood cell (CBC) count reveals a white blood cell (WBC) count of 9000/μL (9.0×10^9/L), absolute neutrophil count (ANC) of 2800/μL, hemoglobin level of 5.5 g/dL (55 g/L), mean corpuscular volume (MCV) of 85 μm^3 (85 fL), platelet count of $420\times10^3/\mu$L (420×10^9/L), reticulocyte count of 8%, and total bilirubin level of 1.0 mg/dL (17.1 μmol/L). Which of the following is the most likely clinical course of this patient's anemia?
    - A. Iron deposition in the mitochondria of erythroblasts.
    - B. Progression to aplastic anemia.
    - C. Progression to leukemia.
    - D. Resolution in 4 weeks.
    - E. Transfusion dependence.
2. A 9-month-old boy is brought to the clinic with pallor and poor feeding. On examination he is noted to have hypospadias and a grade III/VI systolic ejection murmur. No lymphadenopathy or hepatosplenomegaly are seen on physical examination. The CBC count reveals a WBC count of 9000/μL (9.0×10^9/L), ANC of 2500/μL, hemoglobin level of 6.6 g/dL (66 g/L), MCV of 102 μm^3 (102 fL), platelet count of $155\times10^3/\mu$L (155×10^9/L), and reticulocyte count of 0.5%. Which of the following is the most likely diagnosis at this time in this patient?
    - A. Diamond-Blackfan anemia.
    - B. Infant leukemia.
    - C. Severe aplastic anemia.
    - D. Shwachman-Diamond syndrome.
    - E. Transient erythroblastopenia of childhood.
3. A 7-year-old girl is brought to the clinic with petechiae and easy bruising. On physical examination she is noted to have short stature and multiple café-au-lait spots. The CBC count reveals a WBC count of 3000/μL (3.0×10^9/L), hemoglobin level of 9.0 g/dL (90 g/L), MCV of 101 μm^3 (101 fL), platelet count of $35\times10^3/\mu$L (35×10^9/L), and reticulocyte count of 0.5%. Which of the following mechanisms is the most likely cause of anemia in this patient?
    - A. Autoimmune destruction.
    - B. Bone marrow failure.
    - C. Chronic inflammation.
    - D. Complement-mediated hemolysis.
    - E. Viral infection of erythroblasts.
4. A 3-year-old girl is brought to the clinic with fever and oral ulcers. On physical examination, she is noted to have leukoplakia, dysplastic fingernails, and a diffuse reticulated rash. The CBC count reveals a WBC count of 5000/μL (5.0×10^9/L), ANC of 700/μL, hemoglobin level of 9.8 g/dL (98 g/L), MCV of 103 μm^3 (103 fL), and platelet count of $150\times10^3/\mu$L (150×10^9/L). Which of the following best describes the characteristics of this patient's hematologic condition?
    - A. Is likely to be associated with thrombosis and hemolysis.
    - B. Should be monitored for progression to bone marrow failure and myelodysplasia.
    - C. Should be treated with danazol to prevent progression to leukemia.
    - D. Should be treated with glucocorticoids to decrease transfusion requirement.
    - E. Will likely resolve once the cause of inflammation is treated.

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5. A 16-year-old girl has recently been diagnosed as having acquired severe aplastic anemia. Her mother has questions regarding other family members. Which of the following is the most appropriate counseling for this family?
   - A. Distant family members should not be bone marrow donors because they may be silent carriers of disease.
   - B. First-degree relatives should be screened annually because they have an increased risk of acute myeloid leukemia.
   - C. First-degree relatives should be directed donors of blood products because the patient will likely be transfusion dependent.
   - D. Matched sibling donor transplant is indicated only if the patient fails immunosuppressive therapy.
   - E. Siblings should have human leukocyte antigen (HLA) testing to be potential bone marrow donors.

Index of Suspicion

1 Breast Development in a 2-year-old Girl

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EDITOR'S NOTE

We invite readers to contribute Index of Suspicion cases through the PIR manuscript submission system at: https://mc.manuscriptcentral.com/pir.

AUTHOR DISCLOSURE Ms Logan and Dr Kingery have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 2-year 10-month-old girl presents with precocious puberty. Her parents recently noticed breast development and vaginal discharge described as "lotion" in her underwear. They deny any exposure to exogenous sources of estrogen. She does not take any medications or have any significant medical history.

Anthropometrics are notable for height of 37.6 in (95.6 cm) (74th percentile), weight of 31.5 lb (14.3 kg) (65th percentile), blood pressure of 82/51 mm Hg, and heart rate of 95 beats/min. Physical examination findings are remarkable for bilateral breast buds consistent with Tanner stage 2, with Tanner stage 1 pubic and axillary hair, and pink vaginal mucosa consistent with estrogenization. Skin examination is significant for the absence of café-au-lait spots.

Laboratory values obtained at presentation reveal normal thyroid function. Luteinizing hormone and follicle-stimulating hormone levels are prepubertal at 0.1 mIU/mL (0.1 IU/L) and less than 0.2 mIU/mL (<0.2 IU/L), respectively. Estradiol level is elevated at 108.6 pg/mL (398.7 pmol/L). On transabdominal pelvic ultrasonography she has a postpubertal uterine size and shape but normal ovarian volumes for age without evidence of a tumor. Her bone age is advanced at 3 years 10 months. Tumor markers are negative. No lesions consistent with fibrous dysplasia are seen on skeletal survey. Findings from brain magnetic resonance imaging and computed tomography of the abdomen and pelvis are normal. A gonadotropin-releasing hormone (GnRH) stimulation test indicates a prepubertal response.

Repeated laboratory studies performed 5 days after initial presentation reveal that her estradiol level decreased to 35.4 pg/mL (130.0 pmol/L). Further history reveals the diagnosis.

DISCUSSION

Four months after her initial presentation, the patient's estradiol level has decreased further to 8.8 pg/mL (32.3 pmol/L). On physical examination, breast buds have decreased in size, with minimal glandular tissue, and her vaginal mucosa has a red, beefy appearance. Her parents share that the girl's grandmother uses vaginal estrogen cream. The girl had been residing at her grandmother's house while her parents were away to adopt her younger brother. Since she lost access to the cream after her parents' return home, her symptoms have virtually resolved.

Exogenous Estrogen Exposure

Exogenous sources of estrogen are suggested by the history, laboratory values, imaging findings, and near-complete resolution of symptoms. Decreasing estradiol levels support this diagnosis; other pathologies, such as tumors and gonadotropin-dependent precocious puberty (GDPP), or central puberty, typically intensify over time.

Children are particularly sensitive to even small variations in levels of sex steroids. (1) Breast tissue size correlates with circulating levels of estradiol, especially early in life—this sensitivity is present in both girls and boys. (1) Similarly, estradiol has a biphasic effect on bone growth. (1) At low levels, estradiol stimulates linear growth via epiphyseal growth; at high levels, it causes cessation of linear growth via epiphyseal plate closure. (1) It is suggested that estradiol is the primary hormone driving pubertal growth in both girls and boys. (1) Thus, estrogen promotes both increased linear growth velocity and advancement of bone age in children.

Diagnostic Procedures

The keys to diagnosis in this case are a good history and the diminishing estradiol levels. Decreasing estradiol levels in association with gradual resolution of symptoms fostered the likelihood of previous exposure to exogenous estrogen that had subsequently been removed from her environment.

In addition to low gonadotropin levels, the patient's negative response to GnRH stimulation testing makes GDPP unlikely. Measurable or stimulated gonadotropin levels with GnRH stimulation in a child are consistent with GDPP. Pelvic ultrasonography can be helpful to evaluate for increasing ovarian volumes consistent with central stimulation, as well as to rule out ovarian pathologies for precocious puberty such as tumors. Pelvic ultrasonography also allows for evaluation of uterine and endometrium volume, which increases with estrogen exposure. A brain magnetic resonance image to assess for pathology, such as tumors or pituitary abnormalities, is indicated with biochemical evidence of GDPP. However, most GDPP in girls is idiopathic.

An elevated estradiol level in the presence of low gonadotropin levels is suspicious for either peripheral or exogenous estrogen exposure. Tumor markers, pelvic ultrasonography, and computed tomography of the abdomen and pelvis are each useful in detecting an estrogen-producing mass, which can cause estrogenization in the absence of measurable gonadotropin levels. Although primary hypothyroidism with high circulating levels of thyrotropin is a cause of precocious breast development, the patient had normal thyroid function laboratory values.

Differential Diagnosis

In girls with peripheral or gonadotropin-independent precocious puberty (GIPP), an ovarian mass is only one of many differential diagnoses. Long-standing primary hypothyroidism associated with vaginal bleeding and breast development is termed *Van Wyk–Grumbach syndrome.* (2) Girls with primary hypothyroidism may also present with galactorrhea and short stature with primary hypothyroidism. (3) Although a functional ovarian cyst is the most common cause of GIPP, recurrent episodes of breast development and vaginal bleeding would raise the suspicion of McCune-Albright syndrome, which is associated with the classic triad of multiple café-au-lait spots, fibrous dysplasia, and GIPP. (4) If the patient's vaginal discharge had a foul odor, a foreign body should be suspected, although these patients typically do not have breast development or elevated estradiol levels. (5) Last, concern for sexual abuse may be raised in any child with genital complaints, especially vaginal bleeding in the absence of breast development. (6)

Treatment

In most cases of exogenous hormone exposure, removal of the causative agent from the environment allows for regression of induced hormonal effects, as observed in our patient. However, it does not negate the potential long-term complications resulting from exogenous sex steroid exposure early in life; these may include compromised adult height, psychosocial trauma, or increased risk of certain cancers in adulthood. (1)

Lessons for the Clinician

- Although gonadotropin-independent precocious puberty (GIPP) is an uncommon cause of precocious puberty in girls, it is important to recognize because management and expected clinical course vary significantly based on etiology.
- GIPP resulting in examination findings consistent with estrogenization include benign and malignant gonadal tumors, McCune-Albright syndrome, primary hypothyroidism, and exogenous sex steroid exposure.
- Exogenous sex steroid exposure should be considered in any child presenting with gonadotropin-independent precocious puberty.
- Even if parents deny the possibility of exogenous sex hormone exposure, it should remain on the differential diagnosis until definitely excluded. Although sensitive and potentially uncomfortable, it is important to encourage the parents to query each caretaker about potential personal use of exogenous steroids.

References for this article are at http://pedsinreview.aappublications.org/content/39/12/612.

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2 Fatigue and Shortness of Breath in an 18-year-old Girl

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AUTHOR DISCLOSURE Drs Lee and Miller have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

An 18-year-old girl with a history of primary hypothyroidism presents for scheduled follow-up of her hypothyroidism. She has a history of significant mood disorder and psychiatric hospitalizations, and she has been living in a supervised group home for the past several years. She reports a 1-year history of neck swelling and states that she always feels tired at school. She states that she stopped taking her levothyroxine 6 months ago but without explanation and that she does not feel any different since stopping her medication. Her vital signs and examination findings are normal; her thyroid gland is not enlarged. Laboratory values are notable for a highly elevated thyrotropin level of 215.8 IU/L and a low free thyroxine level of 0.30 ng/dL (3.86 pmol/L). She is instructed to resume taking levothyroxine and is provided with an updated prescription.

She returns for a follow-up visit 3 months later. She completed 1 month of treatment with levothyroxine but has not refilled her prescription since then. The group home staff member states that they offer medication reminders to residents but that medication compliance is not mandatory. The patient reports onset of constipation, increasing fatigue, cold intolerance, sad mood, and shortness of breath with exertion. On further questioning, she reports that she feels light-headed and for the past week has had substernal chest pain that is worse with exertion.

Physical examination reveals an obese, alert, interactive adolescent. Her heart rate is 123 beats/min and her blood pressure is 114/56 mm Hg. She has bounding carotid pulses bilaterally. There is no thyromegaly or pretibial edema. Laboratory tests are performed, and after the results are received she is referred to the emergency department for further evaluation and management.

DISCUSSION

Her laboratory values from her office encounter demonstrate severe microcytic, microchromic anemia, with a hemoglobin level of 2.5 g/dL (25 g/L), a hematocrit level of 10.2%, a mean corpuscular volume of 72 μm^3 (72 fL), and a mean corpuscular hemoglobin concentration of 24.8 g/dL (248 g/L). She presents to the emergency department, where her complete blood cell count is rechecked and confirms severe anemia. Her white blood cell count and platelet count were normal. Her thyroid studies are remarkable for an extremely elevated thyrotropin level of 393.40 IU/L and an undetectable free thyroxine level.

Hematology is consulted, and further hematologic and iron studies are obtained to identify the cause of her anemia. Our patient has a reticulocyte count of 1.91%, which is inappropriately normal for her degree of anemia. Iron studies show a normal total iron binding capacity of 423 μg/dL (75.7 μmol/L), a normal transferrin level of 296 mg/dL (36.4 μmol/L), a low iron saturation of 9%, and a low ferritin level of 3.4 ng/mL (7.64 pmol/L)

Our patient receives 2 U of packed red blood cells in the emergency department. Because of her complaint of chest pain, an electrocardiogram (ECG) is performed, which shows sinus tachycardia with T-wave inversions and 1-mm ST-depressions in leads I, II, and aVF and T-wave inversions in leads V4 to V6. Serial serum troponin measurements are obtained and remain negative. Her ECG findings improve after the blood transfusions.

Our patient's anemia is determined to be most likely secondary to poorly controlled hypothyroidism. Levothyroxine therapy is restarted at her previous dose, and she receives an additional 2 U of packed red blood cells for her severe anemia, resulting in an increase in hemoglobin level to 7.9 g/dL (79 g/L) before discharge.

On outpatient follow-up several months later, she reports that she lost her medication shortly after hospital discharge and did not refill her prescription for levothyroxine. She reports generally not feeling well but denies dizziness, cold intolerance, constipation, or fatigue. Laboratory tests are performed, she is restarted on levothyroxine, and she is given strong encouragement to improve adherence to this treatment. Results of her laboratory testing are notable for a thyrotropin level of 112.6 IU/L, a free thyroxine level of 0.40 ng/dL (5.15 pmol/L), and a hemoglobin level of 4.9 g/dL (49 g/L). Outpatient social work is engaged to coordinate disease management with her group home supervisor, primary care physician, and psychiatrist. She subsequently leaves custody of social services and moves out of her group home. Attempts to compel her to return for follow-up care are unsuccessful.

THE CONDITION

Primary hypothyroidism is relatively common, seen in approximately 1% to 2% of adolescents, and is most often caused by autoimmune (Hashimoto) thyroiditis. Hypothyroidism occurs more frequently in females (2:1), and is more common in type 1 diabetes mellitus, Down syndrome, and Turner syndrome. (1) Adequate treatment with levothyroxine normalizes thyroxine and thyrotropin levels and results in good outcomes if diagnosed in a timely manner. Symptoms of untreated hypothyroidism can be variable and include linear growth failure, constipation, fatigue, cold intolerance, and excessive weight gain.

Normocytic anemia is thought to occur in approximately one-third of individuals presenting with hypothyroidism. (2) Some studies suggest that up to 65% of children and adolescents with hypothyroidism may have concomitant anemia. (3) There are multiple mechanisms that may be involved in the development of anemia in untreated or undertreated hypothyroidism.

Erythropoietin production in the kidneys is dependent, in part, on adequate thyroid hormone levels. Thyroxine increases erythropoietin gene expression, thus increasing erythropoietin production. With less thyroid hormone circulating in the hypothyroid state, there is decreased plasma concentration of erythropoietin. Anemia secondary to hypothyroidism is usually normocytic and responds appropriately to thyroid replacement therapy. (4)

The microcytic anemia observed in our patient may also be secondary to iron malabsorption in the gut due to hypothyroidism. Low circulating thyroxine levels lead to decreased iron absorption and decreased iron incorporation into erythrocytes and may affect erythroid progenitor proliferation and differentiation. (5)(6) Hypothyroidism can also induce microcytic anemia via menorrhagia; however, it unlikely that this contributed to our patient's anemia given her use of contraception with medroxyprogesterone acetate.

Although hypothyroidism is typically associated with normocytic anemia, our patient presented with a microcytic hypochromic anemia with an inappropriately normal reticulocyte count. We speculate that her long-standing hypothyroidism caused anemia due to iron deficiency as well as direct effects on erythropoietin production and proliferation of erythroid progenitors. Adequately addressing her anemia may require both adequate thyroxine replacement and iron replacement.

Our patient also presented with chest pain and several abnormal ECG findings that may have not all been related to her anemia. Severe, long-standing hypothyroidism can lead to pericardial effusions and nonpitting edema. This patient's echocardiogram noted a small to moderate circumferential pericardial effusion without hemodynamic significance. Because thyroxine therapy reverses all the cardiovascular changes associated with hypothyroidism, it would be of value to repeat an echocardiogram in the future to see whether this effusion resolves after improved compliance with levothyroxine therapy.

Although we suspect that the patient's anemia was caused by her hypothyroidism, this cannot be confirmed until her hypothyroidism is adequately treated. Although microcytic anemia is commonly found in patients with hypothyroidism, this case illustrates that in cases of prolonged untreated hypothyroidism, the degree of anemia can be severe.

Unfortunately the patient has continued to be poorly compliant with levothyroxine treatment, and despite multiple attempts to recall the patient, she has not returned for treatment of her hypothyroidism and severe anemia. Adolescent patients may respond to a diagnosis of chronic disease with anger, sadness, and denial. Our patient has additional psychosocial stressors, including her mood disorder and residence in a group home, which can increase the risk of withdrawal from active management of her disease. In this case, despite engaging social work and court-appointed guardians to support the patient's medical treatment, we were unable to improve her adherence to medical treatment of her hypothyroidism and anemia. It remains important to identify patients at risk for poor engagement in medical care and to use support systems at the earliest opportunity to optimize outcomes.

Lessons for the Clinician

- Anemia is a common finding in patients with hypothyroidism. There is significant overlap in symptoms of hypothyroidism and anemia (cold intolerance, fatigue, depressed mood), and the clinician should be aware of findings of both anemia and hypothyroidism in patients with concerning symptoms.
- Adequate treatment of hypothyroidism is expected to result in resolution of normocytic anemia. Treatment of microcytic anemia in a patient with long-standing hypothyroidism may also require the addition of iron supplementation.
- Engagement of the adolescent patient in the management of a chronic disease can be a challenge, particularly if other psychosocial stressors are present. Early utilization of support services such as psychology and social work may be helpful in ensuring better compliance and follow-up.

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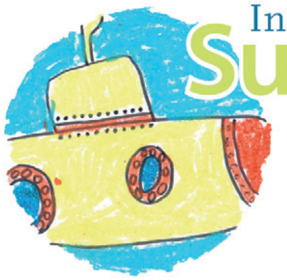

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3 Priapism in a 13-year-old Boy

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AUTHOR DISCLOSURE Drs Clark, Hsu, Darves-Bornoz, Tanaka, Mason, and Katzenstein have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PRESENTATION

A 13-year-old boy without a significant medical history presents with a painful erection that has persisted for 3 days. He denies any known stimulus, trauma, or new medications. He has not had any other symptoms except for vague headaches and leg pain in the past month. He has seen 2 providers in the past 3 days, who prescribed therapies including lidocaine, oral pseudoephedrine, and antibiotics without relief. No laboratory tests were obtained at either visit.

On physical examination he is afebrile, his blood pressure is 146/76 mm Hg, and his heart rate is 117 beats/min. He appears uncomfortable from penile pain but is nontoxic. On abdominal examination, his spleen is palpable 4 cm below the costal margin, and his genitourinary examination reveals an erect penis that is erythematous, tender to palpation, and without any obvious perfusion defects. The remainder of his examination findings are normal.

Pediatric urology is urgently consulted for management of priapism, and laboratory studies are sent, which reveal the etiology of his symptoms.

DISCUSSION

A complete blood cell (CBC) count reveals a white blood cell (WBC) count of 350,000/μL (350×10^9/L), hemoglobin level of 8.5 g/dL (85 g/L), and platelet count of $450\times10^3/\mu$L (450×10^9/L). The differential count includes 67% neutrophils, 5% lymphocytes, 2% monocytes, 1% basophils, 13% metamyelocytes, 9% myelocytes, 1% promyelocytes, and 2% blasts (Fig 1). Levels of electrolytes, blood urea nitrogen, creatinine, liver enzymes, and uric acid are all normal. Flow cytometry of the blood shows granulocytosis with no increase in blasts. Priapism secondary to chronic myelogenous leukemia (CML) with leukostasis is diagnosed.

Clinical Course

Urology performed a penile phenylephrine injection, without improvement. The patient was admitted to the PICU for leukapheresis and was started on

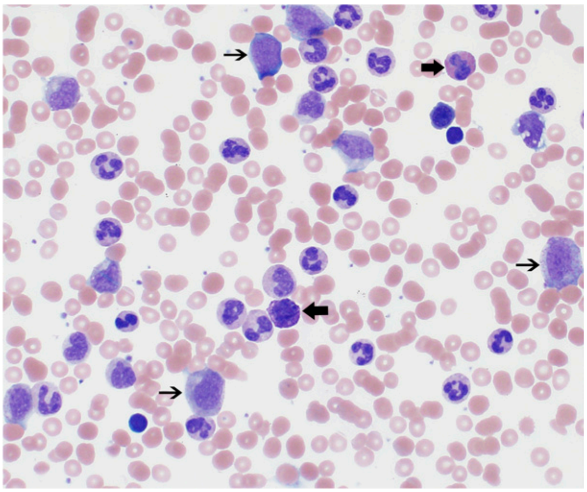

Figure 1. The peripheral blood smear shows a marked leukocytosis consisting predominantly of myeloid elements, including left-shifted myeloid forms (thin arrows) and scattered basophils and eosinophils (thick arrows).

fluids, hydroxyurea, and allopurinol. Leukapheresis was performed with reduction of the posthydration WBC count from 255,000/μL (255×10^9/L) to 222,000/μL (222×10^9/L). Urology then performed corporeal irrigation twice within 12 hours, both with initial detumescence and nearly immediate return of the erection. Bone marrow biopsy was performed, and cytogenetic studies revealed the Philadelphia chromosome, confirming the diagnosis of CML (Figs 2–4). He was started on imatinib, with further improvement of his leukocytosis. He underwent a third corporeal irrigation with a distal shunt procedure 36 hours after the previous irrigation. At the time of hospital discharge, his genitourinary examination was improved but still with some phallus rigidity and tenderness.

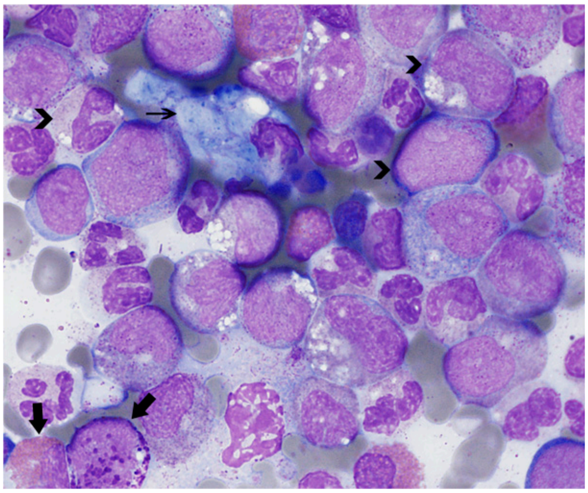

Figure 2. The bone marrow aspirate smear shows myeloid hyperplasia with a full range of maturation (arrowheads) as well as eosinophilia and basophilia (thick arrows) with no increase in blasts. Sea-blue histiocytes (thin arrow) are present. Megakaryocytes (not pictured) include small, hypolobated forms.

The Presenting Condition

Priapism is rare in children but requires urgent intervention. The most common type is ischemic priapism, classified by painful venous occlusion and subsequent tissue ischemia. Much less common is nonischemic priapism, caused by painless high arterial flow fistulization, typically secondary to trauma.

In children presenting with priapism, approximately 65% of cases are attributable to sickle cell disease, and in rare instances, sickle cell trait. Ten percent of cases are secondary to leukemia, 10% are secondary to trauma, 10% are idiopathic, and the remaining 5% are secondary to medications. Of the 10% secondary to leukemia, approximately half are CML.

Management of priapism should involve primary measures of analgesia and attempts to ease the erection with cold packs, urination, ejaculation, and/or physical exercise, along with urgent urologic consultation. Laboratory testing should include a CBC count and electrolytes to assess for common pathologies associated with priapism. When priapism is secondary to an underlying disease process, addressing the primary pathology in addition to performing the necessary urologic procedures is recommended. In patients with sickle cell disease, priapism may be treated with exchange transfusion, although evidence supporting such therapy is sparse. When hyperleukocytosis with leukostasis is present, treatment of the malignancy and/or leukapheresis can be useful in improving symptoms and preventing complications.

Timeliness of care is of utmost importance because ischemic priapism without proper treatment can lead to progressive penile necrosis and fibrosis, with the long-term complication of erectile dysfunction. The likelihood of erectile dysfunction increases with the duration of symptoms. (1)

The Underlying Condition

In children, CML is rare, making up 2% to 3% of all leukemia diagnoses. Its hallmark is the Philadelphia chromosome, an abnormal chromosome 22 that is created by the reciprocal translocation t(9;22)(q34.1;q11.2), which fuses the *ABL* gene on chromosome 9 to the *BCR* gene on chromosome 22. The BCR-ABL fusion protein leads to overproduction of granulocytes at all stages of maturation, resulting in marrow replacement. The treatment of CML has been

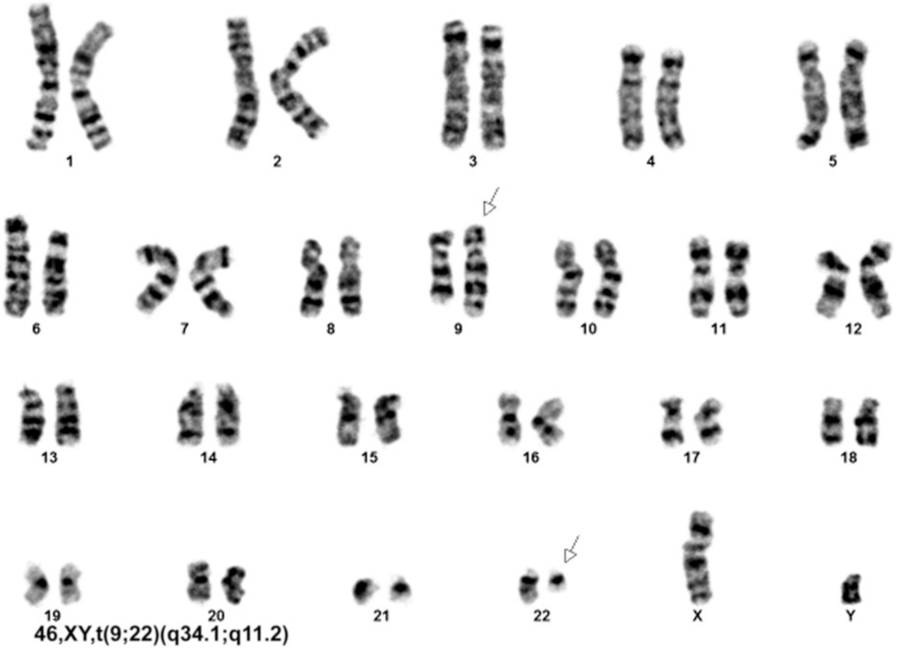

Figure 3. Cytogenetic analysis shows a t(9;22)(q34.1;q11.2) translocation in all 20 cells analyzed. Arrows indicate the abnormal, elongated chromosome 9 (upper arrow) and abnormal, truncated chromosome 22 (lower arrow).

dramatically altered by tyrosine kinase inhibitors (TKIs), which directly inhibit the BCR-ABL fusion protein. Before the use of these targeted agents, stem cell transplant was the only curative option. The optimal length of TKI therapy, the cost analysis of TKI versus stem cell transplant, and the potential consequences of long-term TKI use in children are not completely known.

Children with CML tend to present with elevated WBC counts (median, 225,000/μL [225×10⁹/μL]) without increased blasts. Other symptoms often include fatigue, weight loss, night sweats, and abdominal pain and swelling from splenomegaly. Approximately 10% of patients present with signs of leukostasis, which may include vision changes, intraocular hemorrhages, dyspnea/respiratory distress, headache, altered mental status, hearing changes, aseptic osteonecrosis, and priapism.

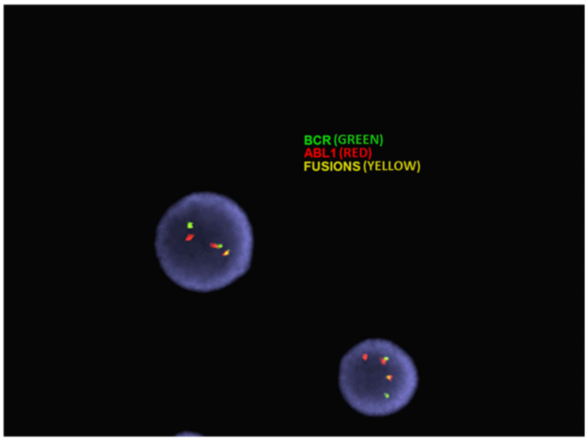

Figure 4. Dual-color–dual-fusion fluorescence in situ hybridization analysis confirms a *BCR/ABL1* rearrangement in 95% of analyzed cells.

Evidence is sparse on the utility of leukapheresis in CML, mainly because cases are rare, but it is generally considered for patients with severe symptoms or evidence of end organ dysfunction, including priapism. In this case, there was minimal change in WBC count and priapism after leukapheresis. (2)

Lessons for the Clinician

- Priapism in a child or adolescent is a urologic emergency and should prompt immediate consultation with a pediatric urologist.
- The most common cause of priapism in children is sickle cell disease, but leukemia should always be considered. Therefore, laboratory tests, including a complete blood cell count and electrolytes, are essential for a pediatric patient presenting with priapism, particularly for those without a history of sickle cell disease or trauma.
- Children with leukemia can present with hyperleukocytosis and leukostasis, which are critical illnesses that require prompt intervention to prevent both acute and chronic morbidity.

References for this article are at http://pedsinreview.aappublications.org/content/39/12/617.

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18-year-old Young Man with Chest Pressure, Shortness of Breath, Fatigue, and Hyponatremia

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AUTHOR DISCLOSURE Dr Finlay-Morreale has disclosed that she was a paid writing fellow for Doximity.com and that stock options were made available at the end of the fellowship. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. Dr. Finlay-Morreale is now Assistant Professor of Pediatrics at University of Massachusetts Medical School, Worcester, MA.

PRESENTATION

An 18-year-old male presents to the emergency department with a 3-day history of chest pressure and shortness of breath. He has a history of pectus excavatum surgery (4 years earlier), juvenile rheumatoid arthritis in remission, and trivial aortic root dilation. As a child he had slightly elevated thyrotropin levels and negative antibodies and briefly took levothyroxine. His heart rate is 91 to 96 beats/min, and his blood pressure (BP) is 100/67 to 110/69 mm Hg. Laboratory results include the following: sodium, 125 mEq/L (125 mmol/L); potassium, 5.4 mEq/L (5.4 mmol/L); chloride, 92 mEq/L (92 mmol/L); carbon dioxide, 24 mEq/L (24 mmol/L); anion gap, 9 mEq/L (9 mmol/L); glucose, 142 mg/dL (7.88 mmol/L); blood urea nitrogen, 33 mg/dL (11.8 mmol/L); creatinine, 0.97 mg/dL (85.75 μmol/L); glomerular filtration rate, greater than 60 mg/dL; troponin I, less than 0.01 ng/mL (<0.01 μg/L); brain-type natriuretic peptide, 6 pg/mL (6 ng/L) (reference range, <35 pg/mL [<35 ng/L]); and D-dimer, 0.31 μg/mL (1.70 nmol/L) (reference range, <0.5 μg/mL [<2.7 nmol/L]). His electrocardiogram is notable for incomplete right bundle branch block (unchanged from earlier) and ST elevation. Findings from chest radiography are normal. After serious cardiac and pulmonary events are ruled out, he is given a bolus of intravenous normal saline and discharged to follow-up with his primary care doctor who he had not seen for three years. Two days later he presents to his pediatrician with the additional complaint of profound fatigue, which precludes even sitting upright for cardiac auscultation. His heart rate is 65 beats/min, BP is 110/78 mm Hg (similar to previous visits), and oxygen saturation is 100%. A review of his growth chart shows drops in weight and BMI during the past 3 years from the 25th to below the 5th percentile. He denies abdominal or back pain, palpitations, and nausea or vomiting. Echocardiography performed later in an outpatient setting was unrevealing. He receives another bolus of normal saline and is referred to the emergency department, where his BP is 88/33 mm Hg. Shortly after, the diagnosis is determined based on laboratory results, vital signs, and presentation, and definitive treatment is given.

Diagnosis

The patient had hyponatremia, borderline hyperkalemia, hypotension, and profound fatigue. Objectively the patient was pale, but with questioning he revealed that his friends had noted that he looked more tan than his usual coloration despite it being winter. A diagnosis of primary adrenal insufficiency (PAI) presenting in adrenal crisis was determined. He was immediately resuscitated with normal saline, blood was collected for corticotropin (it was high) and cortisol (it was low), and stress-dose hydrocortisone was promptly given. Once stabilized in the emergency department he was admitted to the hospital for further management.

The Condition

The adrenal gland produces glucocorticoids, mineralocorticoids, and sex hormones. Primary adrenal insufficiency is rare, with approximately 90 to 140 cases per million in developed countries, and an incidence of 4 to 6 new cases per million per year. (1) Globally, tuberculosis and human immunodeficiency virus remain important causes of secondary adrenal failure. Symptoms of adrenal insufficiency include fatigue, weight loss or failure to gain weight or poor growth, postural dizziness, and anorexia. Patients with primary adrenal failure can have hyperpigmentation, but not always (eg, some fair people with red hair who do not tan), and patients with secondary or central adrenal failure do not have hyperpigmentation. During crises, these symptoms progress to severe weakness, abdominal pain, nausea, vomiting, back pain, confusion, and loss of consciousness. Other signs include hypotension, abdominal guarding, and delirium. Laboratory testing will generally show hyponatremia, hyperkalemia, hypoglycemia, hypercalcemia, and possibly elevated renal and hepatic function tests. In children, approximately 70% of new cases of PAI are due to congenital adrenal hyperplasia (CAH), and 45% are due to autoimmune causes. In adults, 85% are autoimmune in nature. (1)(2) In the United States, CAH (specifically, the 21-hydroxylase-deficient, or "salt-wasting" type) is most often identified on the newborn screen. In contrast, primary autoimmune adrenal failure often goes undiagnosed for years and can present with adrenal crisis during times of stress or illness due to glucocorticoid and mineralocorticoid deficiency. A survey of adult patients found that 60% were evaluated by more than 2 physicians before being diagnosed. The same study showed a median of 2 years between onset of symptoms and diagnosis in children, many of whom presented in adrenal crisis. (3) The definitive diagnostic test for adrenal insufficiency is debated. There is a standard-dose corticotropin stimulation test and a low-dose stimulation test. The former consists of administration of 250 μg of corticotropin being administered (for children ≥2 years of age; 125 μg for children 1–2 years, and 15 μg/kg for infants). Cortisol levels are then checked at 30 and 60 minutes. A cortisol peak less than 18 μg/dL (<500 nmol/L) is a positive result. In some instances, it is thought that a more physiologic dose of 1 μg of corticotropin is more sensitive, and has been advised for cases of secondary or tertiary adrenal insufficiency, recent-onset disease, or mild chronic disease. (1)(4) This patient's diagnosis was made as above, and stimulation testing was not performed. Once adrenal insufficiency has been identified, its etiology should be sought. In infants, CAH is the primary suspect (72% of cases), (1)(2) and it is identified on newborn screen via an elevated 17-hydroxyprogesterone level. Other congenital causes include adrenal dysgenesis syndromes, corticotropin resistance syndromes, cholesterol synthesis disorders such as Wolman disease and Smith-Lemli-Opitz syndrome, and peroxisomal disorders such as X-linked adrenoleukodystrophy. Due to the possibility of the latter condition, a boy with new-onset adrenal failure should have his very-long-chain fatty acid levels examined. There should be a low threshold for consulting genetics and metabolism for recommendations regarding further diagnostic evaluation. Acquired causes of adrenal insufficiency include hemorrhage, trauma, and destruction by tuberculosis, which can be seen on computed tomographic scans. Positive 21-hydroxylase antibodies are seen in 85% of autoimmune patients. (1)(4)(5) Autoimmune adrenal insufficiency was identified in this young man with positive antibody results. Approximately 50% of the time, other autoimmune conditions are comorbid, including autoimmune polyendocrine syndrome type 1 (involving chronic mucocutaneos candidiasis and hypoparathyroidism) and type 2 (involving autoimmune thyroid disease and type 1 diabetes). Assessing for these conditions is recommended in all patients with primary autoimmune adrenal insufficiency. (4)

Management

Management of adrenal crises includes giving 20 mL/kg of normal saline as needed, followed by isotonic maintenance fluids at 1.5 to 2 times the maintenance rate. Electrolyte abnormalities should be corrected per standard protocol. Immediate intravenous administration of 100 mg (50 mg/m^2) of hydrocortisone, followed by 200 mg (50–100 mg/m^2) over 24 hours via continuous drip or 6 hourly boluses should be given. Treatment should not be delayed while testing is performed. (1)(4) When treating crises with stress-dose corticosteroids exceeding 50 mg of hydrocortisone per 24 hours (in adults), a mineralocorticoid is not required. (1) One exception is the patient with both newly diagnosed adrenal insufficiency and newly diagnosed hypothyroidism.

In these patients, the hydrocortisone must be given first or a stable patient may be pushed into adrenal crisis. (5) After diagnosis, younger patients take hydrocortisone and fludrocortisone daily, whereas some older patients can forgo fludrocortisone therapy. During times of surgery, illness, significant exercise, or other such stressors, stress dosing is recommended to prevent adrenal crisis. All patients should carry an emergency wallet card and a hydrocortisone injection kit for use in times of an emergency adrenal crisis. (2) There are no published randomized controlled studies on treatment regimens for PAI in children; most data are on CAH. The clinician is cautioned to avoid overtreatment and undertreatment by adjusting dosing for body surface area. (4)

The patient has now been maintained on hydrocortisone and fludrocortisone, and his energy and sense of well-being have rebounded. He remains thin and has been referred to a nutritionist.

Lessons for the Clinician

- Patients with hyponatremia, fatigue, and poor growth should be evaluated for adrenal failure.
- Adrenal failure can present nonspecifically and can progress to life-threatening adrenal crisis.
- Adrenal crises are medical emergencies and should be promptly treated with hydrocortisone and intravenous fluids.

References for this article are at http://pedsinreview.aappublications.org/content/39/12/620.

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in Brief

Human Metapneumovirus Infection

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AUTHOR DISCLOSURE Drs Vinci and Lee have disclosed no financial relationships relevant to this article. Dr Krilov has disclosed that he has clinical trial grants from AstraZeneca and Regeneron and that he is a member of GlaxoSmithKline's advisory panel on the influenza vaccine. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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Human metapneumovirus (HMPV) is a frequent cause of upper and lower respiratory tract infections in children, immunocompromised patients, and adults. A lipid-enveloped, negative-sense, single-stranded RNA virus, HMPV is a member of the Paramyxoviridae family, which also includes respiratory syncytial virus (RSV) and the parainfluenza viruses. Since its discovery in the Netherlands in 2001 it has been found worldwide, with humans serving as its primary source of infection. It is spread by direct or close contact with infected secretions. Primates other than humans, such as macaque monkeys, develop signs and symptoms of disease after infection with HMPV. Although infection has not resulted from inoculation of HMPV in birds, there is an avian metapneumovirus subtype that commonly infects bird species.

HMPV is composed of genetic groups A and B, which are divided further into 4 subclasses: A1, A2, B1, and B2. Most individuals have been infected by 5 years of age; however, following early infection, immunity to HMPV is weak and does not confer protection from the virus over a lifetime. No single strain has been shown to consistently predominate over others, with variation over both time and location. Studies have shown discrepancies in incidence and prevalence worldwide. Severity of illness does not seem to correspond to viral genotype: although a French study concluded that patients with subtype B were more likely to have abnormal findings on chest radiography, other studies have not shown any differences in clinical manifestations among the 4 different subtypes.

Peak seasonality for HMPV in temperate regions is late winter and early spring, coinciding with the end of RSV season. However, infections are reported throughout the year. Patients hospitalized with HMPV infection tend to be older than children with RSV: a mean of 22 months vs 10 months, which may reflect better protection in early infancy from the transfer of maternal antibodies against HMPV.

Infection of the respiratory tract by HMPV depends on the F protein. A transmembrane fusion protein necessary for entry into host cells, F protein works by binding to integrins on cell surfaces. The viral G, SH, and M2-2 proteins aid in evasion of the host's immune system, just as RSV's NS-1 and NS-2 proteins do. Infection causes mildly erosive and inflammatory changes in airway endothelium, resulting in an influx of lymphocytes and monocytes and causing airway edema. Once infected, patients typically shed the virus for 1 to 2 weeks.

HMPV should be included in the differential diagnosis of any patient presenting with acute respiratory disease. Once infected, an incubation period of 3 to 5 days elapses before clinical manifestations become apparent. Patients then develop signs and symptoms of increased respiratory effort of varying severity. Upper respiratory tract infections are typically characterized by nonspecific symptoms such as rhinorrhea, cough, sore throat, and croup. However, lower respiratory tract manifestations are far more common and more frequently necessitate hospital admission.

Bronchiolitis, pneumonia, and acute asthma exacerbations are the frequent forms of lower respiratory tract HMPV disease in pediatric patients. It is a leading cause of bronchiolitis during infancy, but rates of hospitalization are lower for HMPV than for RSV in children younger than 5 years old.

Less common manifestations include acute otitis media, gastrointestinal symptoms such as vomiting and diarrhea, maculopapular rash, increased liver transaminase levels, and febrile seizures. Acute otitis media may occur with HMPV infection alone or with concurrent *Streptococcus pneumoniae* infection. In adults, HMPV is associated with chronic obstructive pulmonary disease as well as pneumonia and asthma.

Although co-infection with other viruses, such as adenovirus and influenza, is common, it has not been found to consistently result in increased clinical severity of disease. Patients who are immunocompromised or have underlying cardiac and respiratory pathology are at particular risk for severe disease leading to acute respiratory failure with the need for high-flow oxygen support or even mechanical ventilation. These vulnerable patients are also more likely to experience recurrent infection. In a study conducted in South Africa, human immunodeficiency virus–positive children were 5 times more likely to be symptomatically infected with HMPV than were immunocompetent children.

Radiographic findings are generally nonspecific. Because cell culture of HMPV is difficult, confirmation of infection usually depends on antigenic or nucleic acid detection, most commonly by reverse transcriptase polymerase chain reaction on nasopharyngeal swabs.

Treatment is supportive, with most immunocompetent patients reaching a full recovery without specific interventions. As with RSV lower respiratory tract infections, intravenous hydration for patients with decreased oral intake as well as supplementary oxygen as needed are the mainstays of treatment. All patients with HMPV should be placed on contact and droplet precautions to prevent its spread. Meticulous hand hygiene is paramount.

Although 1 report described 2 immunocompromised patients who recovered after treatment with aerosolized and oral ribavirin in addition to intravenous immunoglobulin, to date no controlled trials demonstrate ribavirin's efficacy against HMPV. An RNA polymerase inhibitor, ribavirin is expensive, and its possible adverse effects include hemolytic anemia and fetal teratogenic effects.

The transmembrane F fusion protein has a high sequence identity (>90%) in all 4 subgroups of HMPV, making it an attractive target for the development of vaccines for vaccines for prevention and monoclonal antibodies for prophylaxis and/or treatment. Animal studies have shown that a viral F protein–based vaccine can induce a strong humoral response against HMPV. The F protein has also been used in the development of monoclonal antibodies. Both murine- and human-based monoclonal antibodies have been developed for trials thus far. Of particular note, the human-based antibody provides prophylactic protection against both HMPV and RSV. Other forms of prophylaxis and treatment are also being studied, including live attenuated vaccines, chimeric vaccines, vaccines made from viruslike particles, and fusion inhibitors targeting the F protein.

COMMENT: HMPV and RSV appear to be close cousins, coming from the same Paramyxoviridae family with much in common genetically and clinically. Not surprisingly, then, their responses to therapeutic interventions are also akin. As had commonly been the practice with RSV, a study from Children's National Medical Center found that in 2010, 69% of 207 patients with documented HMPV respiratory tract infection received at least 1 dose of albuterol, but with no effect on outcome. The accumulating evidence that we risk more harm than good has become compelling enough for the American Academy of Pediatrics in 2014 to issue an updated Clinical Practice Guideline for bronchiolitis, making strong recommendations against the use of β-agonists, epinephrine, or corticosteroids in its treatment. Whether for RSV or HMPV infection, the standard of care remains supportive measures.

– Henry M. Adam, MD
Associate Editor, *In Brief*

ANSWER KEY FOR DECEMBER 2018 PEDIATRICS IN REVIEW

Hematuria and Proteinuria in Children: 1. C; 2. C; 3. C; 4. B; 5. D.

The Adolescent with Menorrhagia: Diagnostic Approach to a Suspected Bleeding Disorder: 1. B; 2. E; 3. E; 4. C; 5. A.

Aplastic and Hypoplastic Anemias: 1. D; 2. A; 3. B; 4. B; 5. E.

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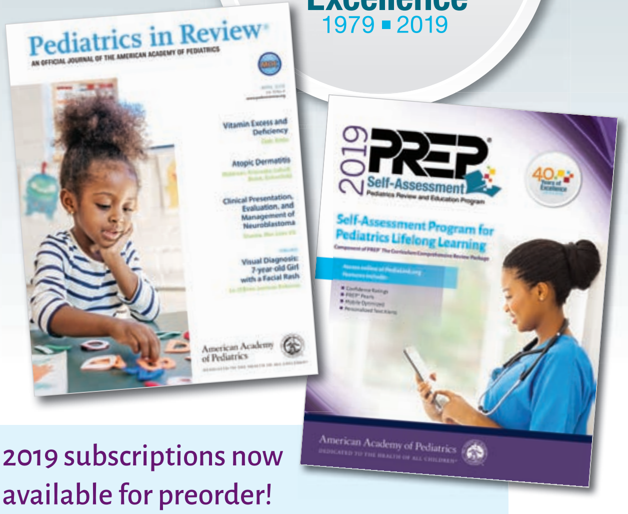
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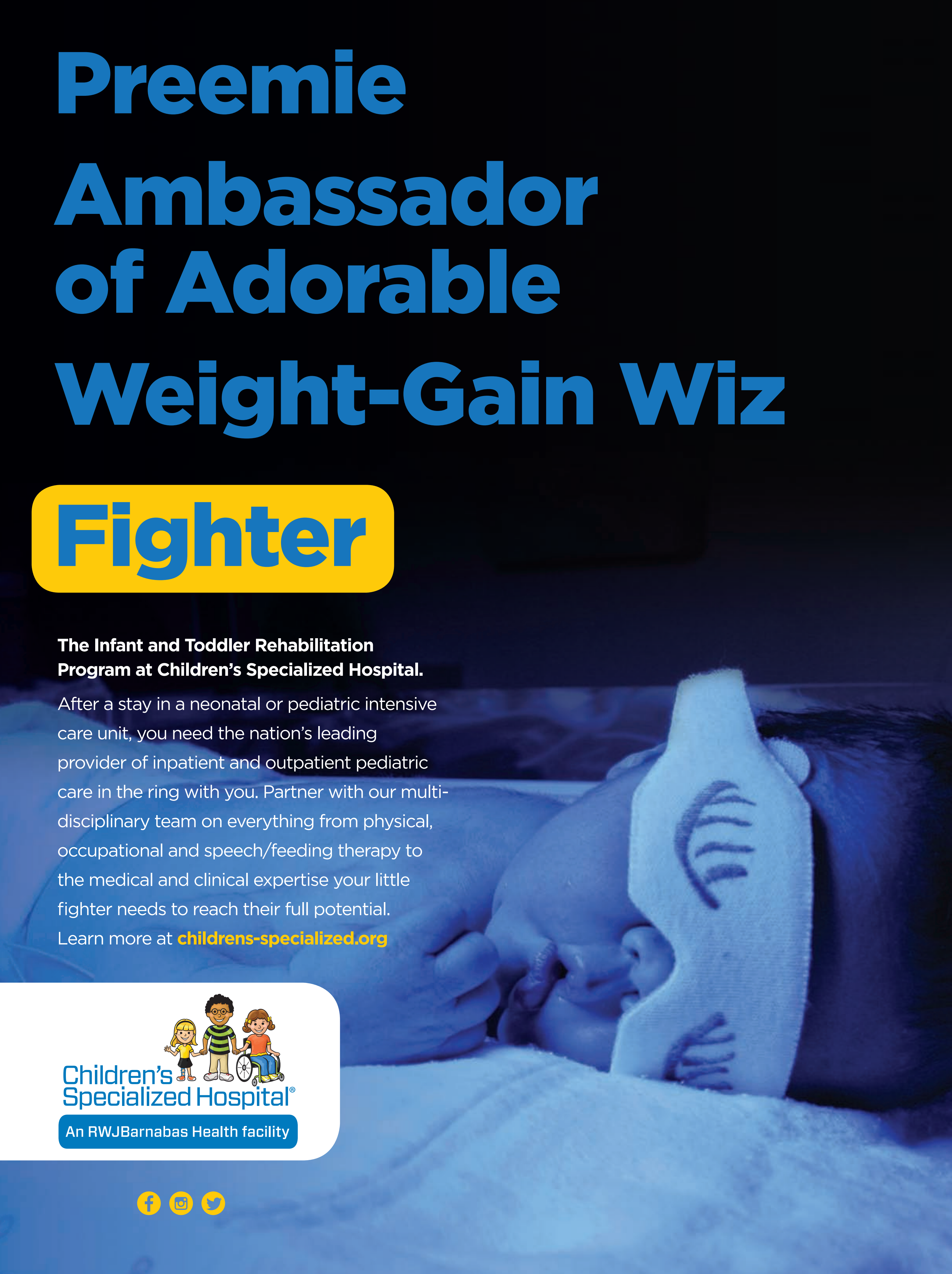

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Visual Diagnosis

A 7-year-old Girl with Labial Edema and Decreased Growth Velocity

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PRESENTATION

A 7-year-old girl presents with a 4- to 6-month history of vulvar swelling of her labia majora. She denies pruritus, pain, or discharge. A review of systems is negative for abdominal pain, diarrhea, constipation, dysuria, fatigue, fever, mouth sores, joint pains, or weight loss. Physical examination of the vulva reveals erythema, edema, and induration of the labia majora bilaterally and clitoral edema but no waxy sclerosis or scarring (Fig 1). There are pink papules in the perianal region without appreciable edema or fissuring. The inguinal folds are normal. Her lips and oral mucosa are normal. A slight 3-month decline in growth velocity is noted from her growth chart. She is initially treated with aclometasone 0.05% ointment, a low-potency topical corticosteroid applied to the affected area of the labia, for a suspected diagnosis of dermatitis. After 2 weeks of treatment, there is no improvement in erythema

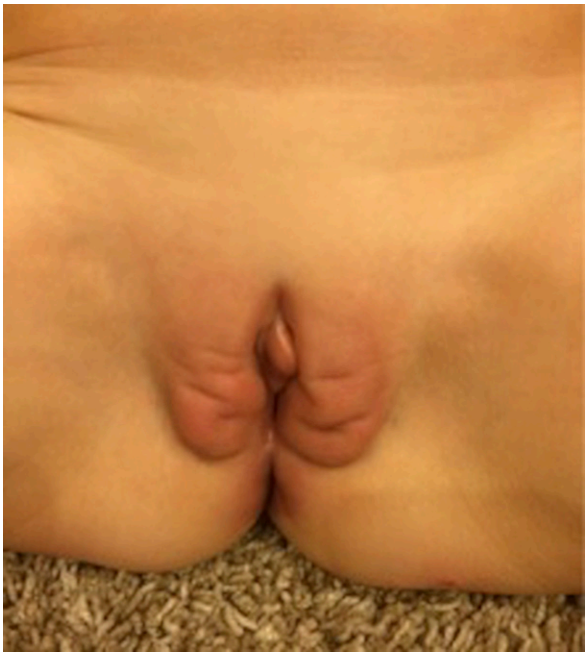

Figure 1. Erythema, edema, and thickening of the bilateral labia majora and clitoris.

AUTHOR DISCLOSURE Drs Riegert, Peebles, O'Connell, and Arkin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

or induration. Ultrasonography of the labia reveals superficial soft tissue thickening with mild hyperemia. Concurrent laboratory evaluation reveals a normal complete blood cell count, a normal comprehensive metabolic panel, a mildly elevated erythrocyte sedimentation rate with a normal C-reactive protein level, and an elevated fecal calprotectin level. A 10-day course of oral cephalexin produces no change. Based on the suspected diagnosis, referral to Gastroenterology is made and a diagnostic colonoscopy is performed.

DIAGNOSIS

The colonoscopy reveals a friable, nodular, and ulcerated terminal ileum. Mucosal biopsies demonstrate patchy architectural disorder, basal plasmacytosis, focal cryptitis, crypt abscesses, and neutrophilic infiltrates in the lamina propria (Fig 2A). There are rare well-formed granulomas. Fig 2B contrasts normal colonoscopy findings. The clinical and histopathologic findings support a diagnosis of metastatic Crohn disease (MCD).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for nontender anogenital erythema and edema in a child is extensive and includes allergic contact dermatitis, irritant contact dermatitis, fixed drug eruptions, paraneoplastic disorders, sarcoidosis, infections, and cutaneous manifestations of inflammatory bowel disease (IBD). A decline in growth velocity may be the first clinical sign of IBD, and supportive laboratory findings may include anemia, hypoalbuminemia, and elevated inflammatory markers, including fecal calprotectin. A thorough history can help differentiate between allergic contact dermatitis, irritant contact dermatitis, and drug eruptions. Diagnosis of IBD is informed by history, review of systems, laboratory tests, and upper and lower endoscopy. Biopsy of the involved skin lesions may be helpful when the diagnosis remains uncertain, but histopathologic findings may be subtle. Typical findings include noncaseating granulomas, but lymphoplasmacytic inflammation and small granulomas may obscure clear diagnosis, and a high index of suspicion from the pathologist is required.

DISCUSSION

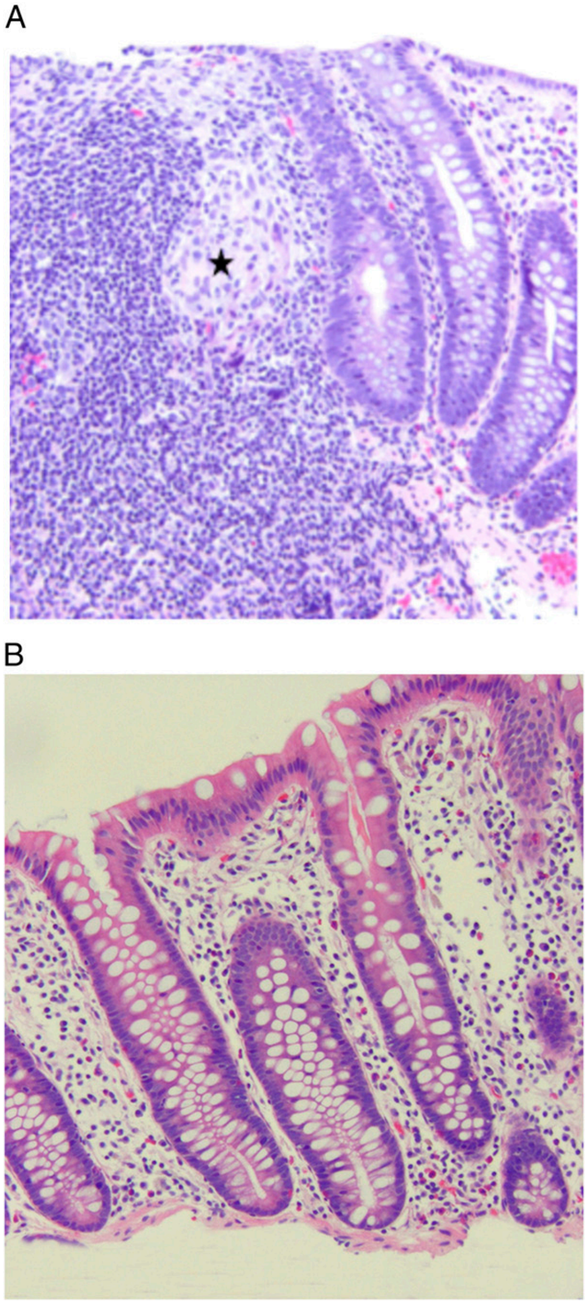

Figure 2. A. Colon biopsy with architectural disorganization. The glands are curved around a dense inflammatory infiltrate in the lamina propria containing a granuloma (star). B. Normal colon histology. The glands are straight and evenly spaced and the lamina propria between the glands contains few inflammatory cells.

Crohn disease presents with extraintestinal manifestations in up to 40% of patients, and the skin is one of the most frequent sites of involvement. Cutaneous manifestations may be subdivided into reactive manifestations of CD, including erythema nodosum, pyoderma gangrenosum, pyostomatitis vegetans, necrotizing vasculitis, aphthous stomatitis, and cutaneous CD, whose histopathology in the skin is identical to that in the gut. In this case, a skin biopsy was deferred given the pathognomonic cutaneous findings, the patient's age, the genital location, and the diagnostic colonoscopy findings. Cutaneous CD at sites distant from the bowel is MCD, whereas contiguous CD is associated with fistulizing disease to the skin. In contrast to adults, recent studies have suggested that 60% to 88% of children with MCD present with skin involvement before gastrointestinal symptoms or a formal diagnosis of gastrointestinal CD. (1)(2)(3) Genital involvement manifests with edema, erythema, knifelike fissuring, and ulcerations of the labia, scrotum, or penis. (3)(4) Similar histologic features in both the skin and gut suggest a shared pathogenesis, originating from an abnormal T-cell response and immune dysregulation. (4) Crohn disease has classically been described as a Th1-mediated process with increased levels of interferon-γ and interleukin-12; however, recent research suggests that interleukin-23 and Th17 may play a role. (4)

There are no consensus guidelines to direct management for MCD. Case reports and small case series have suggested improvement with intralesional steroids, methotrexate, systemic corticosteroids, metronidazole, cyclosporine, azathioprine, sulfasalazine, and tumor necrosis factor α inhibitors (5)(6) However, the treatment course for MCD does not always parallel improvement in gastrointestinal disease, and co-management between Gastroenterology and Dermatology is essential to optimize care. Long-standing, untreated MCD may lead to fibrosis, lymphatic obstruction, and permanent scarring. Early diagnosis and treatment are essential. A high index of suspicion is necessary for children who present with genital edema, with early referral to Pediatric Gastroenterology for evaluation of IBD.

PATIENT COURSE

Treatment with infliximab was initiated, with clinical improvement in her cutaneous disease and normalization of the inflammatory markers.

Summary

- Cutaneous manifestations may be the initial presentation of inflammatory bowel disease.
- Inflammatory bowel disease can be diagnosed by upper endoscopy and colonoscopy with biopsies.
- Treatment for cutaneous manifestations of metastatic Crohn disease is the same as treatment for intestinal manifestations; however, improvement of symptoms may lag.
- Early referral to Pediatric Gastroenterology is crucial when a patient presents with genital erythema and edema that is not due to an easily identifiable, common cause.

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